

THE TREATMENT

of

DIPHTHERIA

by

ANTITOXIC SERUM.

THESIS FOR THE M.D. DEGREE

EDINBURGH UNIVERSITY.

Done entirely by

L. V.



P R E F A C E .

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Diphtheria
William E. Herbert
M.B., Ch. B.
1899

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P R E F A C E .

The following remarks on the Treatment of Diphtheria by Antitoxic Serum, are chiefly based on the experience I obtained in this line of treatment while acting as Assistant Medical Officer at the Edinburgh City Hospital. During that time, I had an opportunity of treating about 90 cases of diphtheria, besides having daily opportunities of observing the treatment and progress of many others.

As so small a number are of little statistical value, I have borrowed where necessary from the most reliable statistics I have been able to obtain. The brief outline on the Preparation and Standardisation of Antitoxine is taken from a standard work on the subject.

GENERAL ARRANGEMENT.

- I. History.
 - II. Statistical Evidence of the Value of Antitoxine.
 - III. Brief Outline of Preparation and Standardisation of Antitoxine.
 - IV. Administration and Dosage of Antitoxine.
 - V. The Clinical Effects which follow the administration of Antitoxine.
 - VI. Antitoxine in the treatment of Laryngeal Diphtheria.
 - VII. Antitoxine in the treatment of "Toxic" cases.
 - VIII. Relation of Antitoxine to Post Diphtheritic Paralysis.
 - IX. Antitoxine in Relation to Albuminuria, Anuria, and Nephritis in Diphtheria.
 - X. Ill Effects following the administration of Antitoxine.
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on diphtheria, and from these two great clinical observers we get the first clear account of the clinical history of this disease. Bretonneau it was, who first practised tracheotomy in laryngeal obstruction of diphtheritic origin. But for the earnest support of Trousseau, however, it is likely tracheotomy would have fallen into disuse, the fate which we shall see later on was to overtake Intubation. The next important advance in the study of this disease, was the discovery by Klebbs, in 1883 of the diphtheria bacillus. It was left, however, for Löffler not only to isolate this micro-organism on artificial media, but to produce in animals, by means of inoculation distinct lesions said by him to resemble diphtheria.

This micro-organism has since borne the name of the Klebbs-Löffler bacillus. On the isolation of the causative bacillus, discoveries followed rapidly.

Roux and Yersin, in 1889 isolated the toxin proper to the bacillus, a discovery which proved beyond doubt, the specific character of the bacillus, doubted at that time even by Löffler³ himself. Names too numerous to mention might be quoted in connection with their work on this subject. Possibly/

ibly it was the almost universal distribution of the disease, its slight regard for age, or sex, or person; the alarming rapidity with which it will attack whole families, and its high mortality, that concentrated such a wealth of intellect on this disease, for certain it is that no other can claim such a host of scientific workers.

In December 1890 Behring and Kitasato made the important announcement, that they had succeeded by means of the blood serum of immunised animals, not only in protecting animals against Diphtheria, (Behring) and Tetanus (Kitasato), but also of curing them when previously infected.

To the works of Behring, Ehrlich, Arouson (who first immunised horses) Roux and Martin, we owe the present treatment of diphtheria by Antitoxine. Roux⁴ it was who first brought the new treatment prominently before the medical world by his paper, read before the International Congress of Hygiene at Buda Pest in 1894. In this address Roux outlined the work done by Behring and others in serum therapy; and gave his results on the treatment of diphtheria by antitoxine - results which at once arrested the attention of the medical world.

OUR PRESENT POSITION:

It has been truly said that of no other disease is our knowledge more complete. This being so, it would hardly have been expected that diphtheria should have increased as rapidly as it appears to have done of recent years. Whilst all other infectious diseases notably typhus, scarlet and enteric fevers have, under improved sanitary conditions, shown a marked tendency to decrease, diphtheria has on the other hand shown a greater tendency to increased prevalence all over the world. Accurate statistics are difficult to obtain over a long period of years, but the following table shows the state of affairs during the last five years in this country.

Table showing the number of cases of Diphtheria notified, in the towns mentioned during the last five years:-

	1897	1898	1899	1900	1901
Edinburgh	214	269	279	483	542
Glasgow	462	433	465	540	563
Liverpool	430	554	793	709	869
Manchester	150	196	248	337	460
Brighton	154	311	541	548	567

It will thus be seen that in the towns mentioned above, there has been a rapid increase in the number of cases of diphtheria notified during the last five years. This increase cannot, of course, be confined to towns specially mentioned. For instance, Brighton only suffered in general epidemic increased prevalence present over the South East of England and London. It is not intended to discuss the many reasons set forth to explain this increase, but it is important to remember the fact in connection with statistics to be produced later on in connection with the antitoxine treatment.

Previous to the introduction of Antitoxine in 1894, the medical press in this country expressed no small amount of alarm at the greatly increased prevalence of diphtheria and at a death rate, which to use the description of the Registrar General could only be described as "formidable". The result of the new treatment evidently caused so great a sense of relief to the medical mind, that it has obscured to a certain extent the fact that diphtheria is now more prevalent than it ever was, and chiefly on that account the total death rate has not been materially affected since the introduction of the antitoxine.

The/

The following table kindly supplied by the Registrar General shows the total death rate in England and Wales since the year 1892.

Year	Total Deaths
1892	6,552
1893	9,466
1894	8,774
1895	7,895 <u>Antitoxine Year.</u>
1896	8,993
1897	7,654
1898	7,661
1899	9,295

It will thus be seen that the total mortality from Diphtheria is subject to comparatively narrow variations, and that the mortality since 1895, when antitoxine was first extensively tried, shows no appreciable change. Is then, this antitoxic line of treatment in diphtheria devoid of any marked improvement on former methods? This question we shall try to decide in the following remarks.

II. STATISTICAL EVIDENCE OF THE VALUE OF
ANTITOXINE.

The year 1895 may be taken as the first year, in which antitoxine was extensively used in the treatment of Diphtheria. It has thus been on trial of over six years. Sufficient time has elapsed, and a sufficiently large number of cases have been treated with the antitoxic serum to define its position as a therapeutic agent. After its first introduction, its reception into this country was of a varied character. Coming as it did at a time, when the popular and medical mind, was alike anxious at the increasing mortality from diphtheria, it was welcomed and received as it were, with "open arms". Very soon results were to justify its reception.

The sound scientific basis of the new treatment, together with the publication of results never before obtained in this country, soon gave this method the first, if not the only place in the treatment of diphtheria. Opponents were, however, not a few. Dr Lennox Brown⁶, one of the most eloquent, has gone to no small trouble not only to show the uselessness of the new drug, but also its actual danger.

Caution/

Caution and even prejudice marked the attitude of many, mindful of the results obtained by a very similar line of treatment in tuberculosis.

Turning now to the "brute force of figures", as Professor Virchow has it, what can statistics show in favour of the new treatment?

Amongst the first to publish his results and express approval, was no less an authority than Professor Baginski.⁷ Between the 15th March 1894 and a corresponding date of the following year he had treated 525 children, under the age of fourteen, of whom 83 or 15.6% died. During part of this time, however, his supply of serum failed, when 126 children were treated on the former lines, of whom 61 or 48.4% died. On the serum treatment being again resumed the mortality again fell.

Dr Clubbe⁸ reports his results at the Childrens' Hospital in Sydney, Australia. At this Hospital, 300 cases were treated with antitoxine, and 300 on the former lines. Of the 300 treated with antitoxine, 60 died, and 240 recovered, a death rate of 20%. Of the 300 treated without antitoxin, 158 died, and 142 recovered; a death rate of 52.6%. In this country, perhaps the most complete and exhaustive statistics to be found, are contained in the/

the Metropolitan Asylums Board Reports for 1896. This report, which is signed by the medical superintendents of the various hospitals under the Board's control, closes with this among other conclusions, "that the combined general mortality is reduced to a point below that of any former year." Table I. shows the marked decrease in the mortality from diphtheria after the introduction of antitoxine.

TABLE I.

showing the mortality from diphtheria in the Hospitals of Metropolitan Asylum Board.

1892	1893	1894	Antitoxine		
			1895	1896	1897
29.5	30.4	29.2	22.8	21.2	17.6

It is interesting to note that the mortality is not due to any alteration of the age of the patients treated, for Table 2 shows that it is in children under five years of age, that the best results were obtained. All are agreed that it is during this period of life that diphtheria is most fatal.

TABLE 2.

Showing base Mortality of Diphtheria in children under five years of age, at the Hospitals of Metropolitan Asylum's Board.

1892	1893	1894	Antitoxine		
			1895	1896	1897
51.5	53.3	43.9	33.5	30.3	24.9

It will thus be seen that it is from hospital experience that the most favourable results have been obtained. In this light Table 3 is of interest.

TABLE 3.

Showing Case Mortality of Diphtheria in London.

	1892	1893	1894	Antitoxine		
				1895	1896	1897
mortality % of all cases notified	23.8	24.5	24.7	21.2	19.9	17.4
mortality % of cases admitted into M.A.B's Hospitals	24.8	27.1	25	18.3	17.7	14.9
mortality % of notified cases not admitted to Hospital	21.5	23.7	24.5	23.3	21.3	20.1
percentage of notified cases admitted to Hospital	30.1	24.5	38.8	41.5	39.9	51.4

With reference to Table 3, it must be allowed, that in 1892, 1893, 1894, a smaller percentage of cases were admitted to hospital; which were probably the worst cases. In these years it will be noted, the hospital results were not only worse than those obtainable/

tainable outside, but were worse than the total percentage mortality of all notified cases. With the introduction of antitoxin a marked change took place. The hospital percentage mortality fell much below the total percentage mortality, while the per cent mortality of cases treated outside remained practically uninfluenced. It will thus be seen that the improvement could not have been due to any local diminution in the virulence of the disease. Uniformly favourable statistics from all parts of the world disprove such to be the case.

The most common "excuse" put forward to explain the improved results of later years is that with advanced bacteriological knowledge and facilities, the diagnosis of diphtheria has been revolutionised, and that cases of a mild nature are now included under, and treated as diphtheria, which formerly would have been excluded. Granted this is so in many cases, it is not applicable to young children, nor to cases of laryngeal diphtheria, where antitoxine produces its most brilliant results.

Furthermore, the bacteriological diagnosis of diphtheria so fashionable at the present time, has a most adverse influence on the results of this line of/

of treatment. Bacteriological examination requires time; and this time wasted puts as many cases beyond the full benefit of antitoxine, as it causes cases of a mild nature to be included to its favour.

Moreover, if we consider carefully the nature of diphtheria, and the real causes of death from it, we are somewhat at a loss to see how a bacteriological examination can decide which may be a mild, and which a severe attack. Is it not more likely that this new treatment "nips in the bud" as it were, many cases arising from a small focus of infection?

A digression may perhaps be permitted here, to strongly deprecate the "wholesale surrender of the clinical fortress", such as the late Professor Kanthack¹⁰ suggests in the following remarks:-

"The Klebbs Löffler Bacillus is found in every case of diphtheria; and from the results of investigations made, we may say, all over the world, we must refuse to call any lesion diphtheria unless it is associated with the bacillus; conversely, any morbid process accompanied by this organism is diphtheria. Formerly, when physicians relied for their diagnosis merely on inspection of the affected parts, or on certain symptoms and signs, cases were excluded/

excluded because they did not conform to the clinical "type", and the absence of gangrene, necrosis or membrane was almost sufficient for a denial of diphtheria.

Bacteriology has taught us we must alter our views, and include under diphtheria many cases which, according to the older conception, would not have been called diphtheria. At the present time, we frequently hear that typical bacilli have been discovered in cases which clinically are not diphtheria. Our clinical notions must, then, be amended and our position reconsidered.....We possess then in this organism of Klebbs Löffler a certain test with the help which in competent hands, it is easy to decide the true nature of a suspicious case and the vexed discussion of the identity or non identity of croup and diphtheria cases henceforth. In tubercle and diphtheria the bacillus asserts itself with an authority which must put aside any preconceived notions."

A full appreciation of the value of the early administration of antitoxine will never allow of such a divorce of clinical and bacteriological observations. If the former clinical standard of diagnosis was inadequate to its intentions, a purely bacteriological one may be equally so to a more dangerous extent. The Metropolitan/

Metropolitan Asylum's Board Report shows that 4.5% of the cases clinically diphtheria received no bacteriological confirmation. Amongst these cases the mortality was 27.7% or nearly 7% higher than the total mortality for the year from diphtheria.

In practice, unfortunately, the great expense of antitoxine must too often be taken into account. However, it must be remembered to get the greatest benefit from antitoxine it must be administered early, as will be shown later. If this is so, from a practical point of view, the diagnosis must be essentially clinical, and the benefit of the doubt given to antitoxine. A bacteriological verdict will be welcome and useful afterwards.

III. BRIEF OUTLINE OF THE PREPARATION AND STANDARDISATION OF ANTITOXINE

For therapeutic purposes, the anti-diphtheritic serum is now solely obtained from the horse; firstly because this animal is able to yield a large amount of serum at one time; and secondly, because in the majority of cases, the serum of the horse has a less injurious effect on the human subject than have the sera of other animals.

PREPARATION:

An active type of the diphtheria bacillus is necessary. Its toxins are obtained from filtered broth cultivations. A small amount of toxine is, from time to time, injected into the subcutaneous tissues of a horse, which is thought to be suitable and free from disease.

The dose of toxine injected at first is small, about 1 c.c. Gradually the amount is increased, at variable periods according to the amount of re-action shown by the animal. From time to time, a small quantity of blood is withdrawn and the antitoxic power of the serum tested. When the requisite standard is reached, the hair is shaved from the horse's neck, the skin rendered antiseptic, and a canula is plunged into/

into the jugular vein, rendered prominent by pressure below the intended seat of puncture. The canula is connected by an india rubber tube with a glass flask, all rendered thoroughly aseptic. When the flask is full, the neck is sealed in a gas flame, and it is then set aside until the serum settles. It is then filtered, rendered antiseptic by the addition of a small amount of such an antiseptic as carbolic acid and is ready for standardisation and use.

STANDARDISATION:

For actual use in the preparation, as well as in the standardisation, toxins and not the living bacillus are always used. The principle of the first method of standardisation as suggested by Behring was briefly as follows:- By experiments the smallest fatal dose of a known toxine was ascertained. A second set of experiments was then made to ascertain the smallest amount of antitoxine, which would neutralise ten times the minimal fatal dose of toxin. Ten times this amount was taken as the unit of antitoxine. In other words, the antitoxic unit was taken to be, ten times the amount of antitoxine required to antagonise a tenfold fatal dose/

dose in a guinea-pig weighing 300 grms. With this standard however, it was found that the same serum when tested with different samples of toxins gave different results.

Ehrlich has endeavoured to explain this difficulty, and to devise a method of Standardisation, which gives uniform results. Ehrlich's experiments and the results he arrived at are here quoted in the words of Dr Wasbourn⁹.

"In the first place he (Ehrlich) discovered "that filtered broth cultivations, or toxines, as "they are usually denominated, contain, in addition "to the true toxines, other bodies which are not "poisonous, but which are capable of combining with "antitoxines."

"Secondly, he found that in a filtered broth "cultivation which had been kept for some time, "these bodies, which he called toxoids, and toxines, "increased at the expense of the true toxines, and "that they were derived from a splitting up of the "latter. He arrived at these conclusions in the "following manner. He took a filtered broth cultivation and estimated by the usual method the "minimal fatal dose, which he designated T. Now "one unit of antitoxine, which we will designate I, "is/

"is supposed to exactly neutralise 100 fatal doses
 "of toxine (100 T.). This amount of toxine we will
 "designate Lo. Consequently Lo, when mixed with I,
 "would form a mixture which produces neither oedema
 "nor other ill effects when injected into the sub-
 "cutaneous tissues of a guinea-pig. I+ Lo repres-
 "ents all inert mixture containing neither free anti-
 "toxine nor free toxine. Ehrlich took such a mix-
 "ture and ascertained by experiment, the amount of
 "toxine which, when added to it, was just sufficient
 "to cause death after injection into a guinea-pig.
 "This quantity of toxine he called D; which we should
 "theoretically expect to correspond to T, the minimal
 "fatal dose. The whole of the toxine in the mixture
 "he called L+. An example will make the matter
 "cleared:- The minimal fatal dose (T) of a toxine
 "was found to be 0.01 c.c. Therefore 1 c.c. con-
 "tains 100 T (Lo) and theoretically we ought to have
 "the following:-

$$\begin{aligned}
 T &= 0.01 \text{ c.c.} \\
 L+ &= 1.01 \text{ c.c.} = 101 T \\
 Lo &= 1.00 \text{ c.c.} = 100 T \\
 \text{Difference } D &= 0.01 \text{ c.c.} = 1 T.
 \end{aligned}$$

"But by experiment it was found that in order to
 "cause death, it was necessary to add, not 0.01 cc.,
 "i.e., one minimal fatal dose, to the neutral mixture
 "(1+ Lo) but 1.01 cc., i.e., 101 fatal doses.

"We/

"We thus get -

$$\begin{aligned} T &= 0.01 \text{ c.c.} \\ L+ &= 2.01 \text{ c.c.} = 201 T \\ L_0 &= 1.00 \text{ c.c.} = 100 T \\ \text{Difference } D &= 1.01 \text{ c.c.} = 101 T \end{aligned}$$

"Ehrlich explained this by supposing that the filtered broth cultivation contained an equal quantity of toxine and non-poisonous toxone. In the neutral mixture one half of the unit of the antitoxine was combined with 100 fatal doses of toxine, and the other half with an equivalent quantity of toxone."

"The toxone possessed a less affinity than the toxine for antitoxine. Consequently, when fresh toxine was added to the mixture, it united with the antitoxine previously united with the toxone, and it was not until 101 fatal doses of toxine were added that a single fatal dose of toxine was free in the mixture. The neutral mixture = 100 antitoxine - toxine + 100 antitoxine - toxone. On adding 101 fatal doses of toxine containing an equivalent quantity of toxone, we get in the mixture 100 antitoxine - toxine + 100 antitoxine - toxine + 100 toxone (liberated) + 101 toxone added + 1 toxine free. It follows from this view that the unit of antitoxine, instead of representing the/

"the quantity of antitoxine which neutralises 100
"fatal doses of toxine, really neutralises 200
"fatal doses, as it neutralises 100 fatal doses of
"toxine plus an equivalent quantity of toxone. We
"must therefore consider that the unit of antitoxine
"is the quantity of antitoxine which completely
"neutralises 200 fatal doses of toxine or their
"equivalent."

"Ehrlich also found that one unit of antitoxine
"neutralised exactly the same quantity of filtered
"cultivation whether the latter was fresh or old,
"although the old cultivation contained fewer fatal
"doses of toxine. From this, he inferred that the
"toxine was split up into toxones having the same
"neutralising power as the toxines."

"By a series of calculations based on a very
"large number of experiments, he was able to deter-
"mine exactly how much toxine and how much toxone
"was present in any filtered cultivation. He was
"also able to demonstrate the presence and to estim-
"ate the amount of, two other bodies, which he call-
"ed toxoids, and which possessed one an equally and
"the other a greater, affinity than the toxine for
"antitoxine. He has shown it is possible to
"standardise/

"standardise antitoxine with a filtered cultivation
"whose composition was unknown. However, such a
"determination would involve a larger series of
"experiments and a careful calculation. Fortunately
"ly a much simpler method is available. The method
"is as follows:- In the German Testing Department
"in Berlin, dried antitoxic serum containing 1700
units per gramme is preserved in sealed bottles.
"This standardised antitoxine is supplied to the
"various laboratories, and the potency of any serum
"can be ascertained by experimentally comparing the
"two. For this purpose two sets of experiments
"are necessary. In the first series, a unit of
"the standard antitoxine is mixed with measured
"quantities of the toxine, and the mixture injected
"into the subcutaneous tissue of a guinea-pig, each
"weighing 300 grms. In this way, is ascertained
"the largest quantity of toxine which can be neut-
"ralised by a unit of the antitoxine. (The
"criterion of neutralisation is the survival of
"the animal for four days, the absence of oedema
"at the site of inoculation not being reliable.)
"Such a quantity is taken to be the test dose of
"the toxine. With the test dose of toxine thus
"determined, another series of experiments is per-
"formed/

"formed. Varying quantities of the serum whose
"potency we are testing are mixed with the test
"dose, and the mixture injected into guinea-pigs.
"The smallest quantity of serum which neutralises
"this test dose contains one unit of antitoxine,
"for it possesses the same neutralising effect as
"a unit of the standard antitoxine. Should the stan-
"dard unit be at any time lost, it can be regained
"by a complicated series of experiments as already
"explained."

IV. ADMINISTRATION OF ANTITOXINE.

Subcutaneous injection constitutes the only means of the therapeutic application of antitoxine.

The rapid manner in which the throat condition improves after the administration of antitoxine, has prompted its use as a local application to the throat, in the belief, that it must have some direct bactericidal action on the Klebbs-Löffler bacillus. This is quite erroneous. Behring⁹ in introducing his antitoxine denied it to have any direct bacteriocidal action, adding that the bacillus would flourish with unabated virulence in the antitoxine serum itself.

Escherich⁹ has shown that antitoxine is useless when administered through the alimentary canal.

He believed it to be destroyed in the liver, for he found it did not get into the general circulation of a dog when injected into the wall of the intestine, between the folds of the mesentery, yet it appeared in the blood when injected subcutaneously.

Thus, subcutaneous injection is the only method of administering this drug. To do this, the skin over the selected area is rendered thoroughly aseptic. This preparation should be thorough, so that later on, some/

some confidence may be placed in it, for the appearance of a rash round the seat of injection, as will be seen later, is not uncommon. The site selected, should be one where the skin is lax, and which can be kept clean in infants, thus the buttock is not a good position, nor is the anterior abdominal wall, as so often suggested.

The best position is into the loose subcutaneous tissues between the shoulders. Here large doses can be introduced without pain. Lying on the site of injection causes no inconvenience, while it aids diffusion, and promotes absorption. Moreover, children and neurotic girls do not see what is going on if this site is selected. If the patient is too ill to turn over with safety, the loose tissue of the breast may be selected.

For means of administration, the best syringe supplied at the present time is, I believe that supplied by Parke, Davis & Coy. It is cheap, can easily be rendered aseptic, and does not readily get out of order.

SELECTION OF AN ANTITOXINE:

Of the many brands in the market, one should be chosen, which is guaranteed to have been recently manufactured, which is aseptic, and which is highly concentrated, i.e., one which contains a large number of antitoxic units per c.c. of serum.

DOSAGE:

A very considerable diversity of opinion still exists on this important question.

In the "Asylums Board Report" the following general rule is laid down. "For ordinary mild cases on the first day, 2000 units is enough; but where, as sometimes happens, the symptoms have progressed very rapidly, even in a few hours a larger amount must be given. In severe cases when first seen, the rule must be to give 8000 to 12000 units, followed by another 2000 to 8000 units every 12 hours for the next 24, or 48 hours or longer, according to the gravity of the case, and the persistence of local exudation."

Dr Washbourne⁹ says "In cases of moderate severity, a dose of 5000 units should be given at once, and should be repeated two or three times at intervals of twelve hours, according to the progress of the case. In severe cases, or in cases treated late in the disease, the dose should be 8000 to 10,000 units, which should be repeated at the same intervals, as in the cases of moderate severity."

In my own series of cases the working standard adopted was; for cases of moderate severity if seen

on -	1st day of disease	=	2000 units
"	2nd " " "	=	3000 "
"	3rd " " "	=	4000 "
"	4th " " "	=	6000 "

In/

In all severe cases, laryngeal cases and toxic cases the rule was to give an initial dose of ~~from~~ 6000 to 8000 units.

The conclusion drawn from my experience in these cases is, that the dose was too small. This is suggested by the number of times the dose had to be repeated; and by the longer average time the throat symptoms took to clear up, than is recorded by those, using larger doses.

M'Collom¹² advocates the use of large doses of antitoxine, and quotes cases in which he has used enormous doses. The first was a boy aged 6, who gained relief from 56,000 units, which was administered within four days. No bad results followed. A second case, a girl aged 6, had 80,000 units with successful results. Other cases had 60,000, 84,000, 56,000, 76,000 and 92,000 all of which recovered. To the use of such doses he attributes the recovery of many apparently hopeless cases.

No hard and fast rules can be laid down, but the following considerations may be taken as a guide.

1. Age of the patient:

The age of the patient may safely be disregarded. In adults a majority of cases recover. In children the younger the child (after 1st year) the greater the tendency to death from diphtheria; thus the greater the necessity for large doses administered early in children.

2. The day of the disease:

The greater the area of throat affected with membrane, the greater should be the dose.

4. In all cases of laryngeal and nasal diphtheria the dose should be large.

5. The history of the case:

The more rapid the progress of the case, especially if associated with a small irregular pulse and a pallid, anxious expression, the larger should be the dose.

V. THE CLINICAL EFFECTS WHICH FOLLOW THE
ADMINISTRATION OF ANTITOXINE.

These may be divided into,

1. Effects on the Local Condition.
2. Effects on the general Constitutional Condition.

The local effects comprise,

- (a) Arrest of the active process of the disease.
This is chiefly manifested by the arrest of the formation and spread of the false membrane.
- (b) Earlier detachment of the membrane already formed.
- (c) Diminution of the local swelling and irritation.

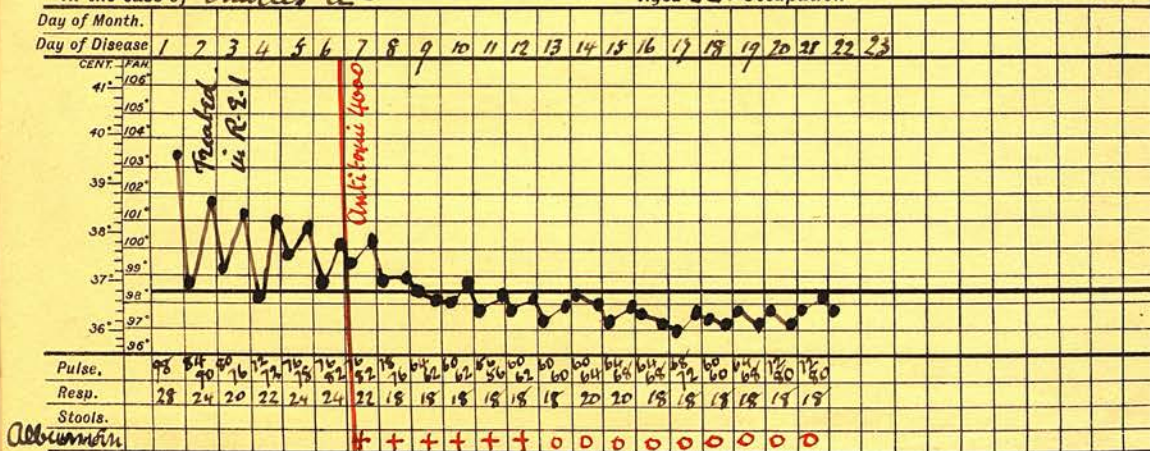
It is chiefly in cases of laryngeal diphtheria that the above clinical effects of the usefulness of antitoxine are manifest.

Cases of faucial diphtheria, however, show the same thing in a less striking manner. The effect on the membrane is to soften and disintegrate it. It thus loses its tough leathery appearance so often assumed and becomes softer, and more pulpy; thus enabling it to be easily removed by a swab; nor is the same raw, angry looking surface left behind, that is usually seen when diphtheritic membrane is removed from the throat.

CASE 1. /

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of *Charles A-* Aged 22. Occupation

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CASE 1. Extensive faucial Diphtheria.

Charles A. age 22, was admitted to the City Hospital on June 1st, 1900. He had been kept under observation in the R.I.E., because repeated bacteriological examinations had failed to reveal presence of the Klebs-Löffler bacillus. Both tonsils, anterior pillars of the fauces, and uvula, were covered with a thick tough looking membrane, which could not be removed with a swab. The urine contained albumen. The membrane on the throat was said to be spreading more rapidly during the two days previous to admission.

4000 units of antitoxine were administered. Next day the membrane appeared softer. The following day the throat condition was much improved, and on the fifth day after admission the throat was quite clean. This throat had been subjected to energetic local treatment for five or six days previous to admission to Hospital.

The effect of antitoxine on the throat condition varies considerably. In some cases a dose of 4000 will rapidly clear the membrane from the throat, in other cases, 12,000 to 20,000 units will be required to have the same effect.

Chart 1

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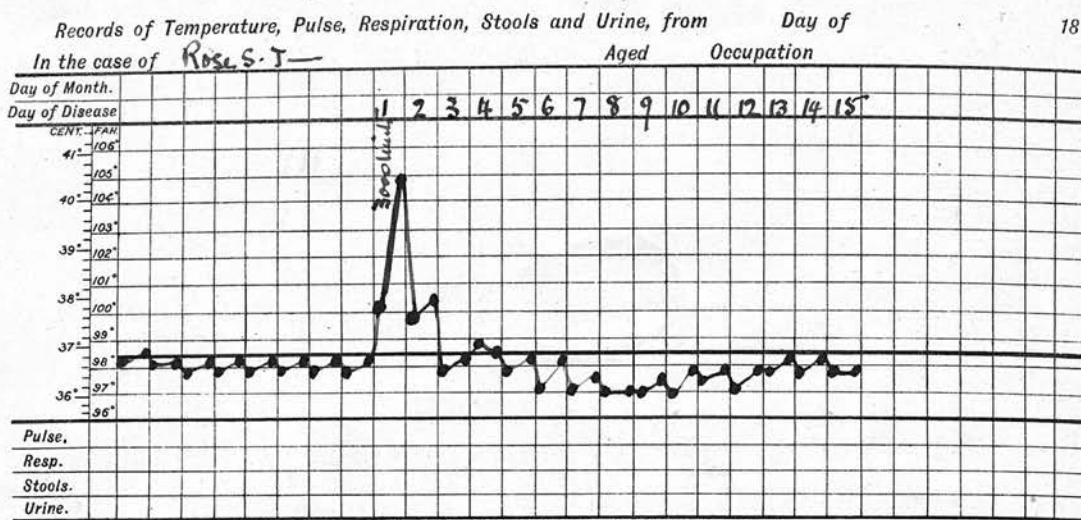


Chart 2

12

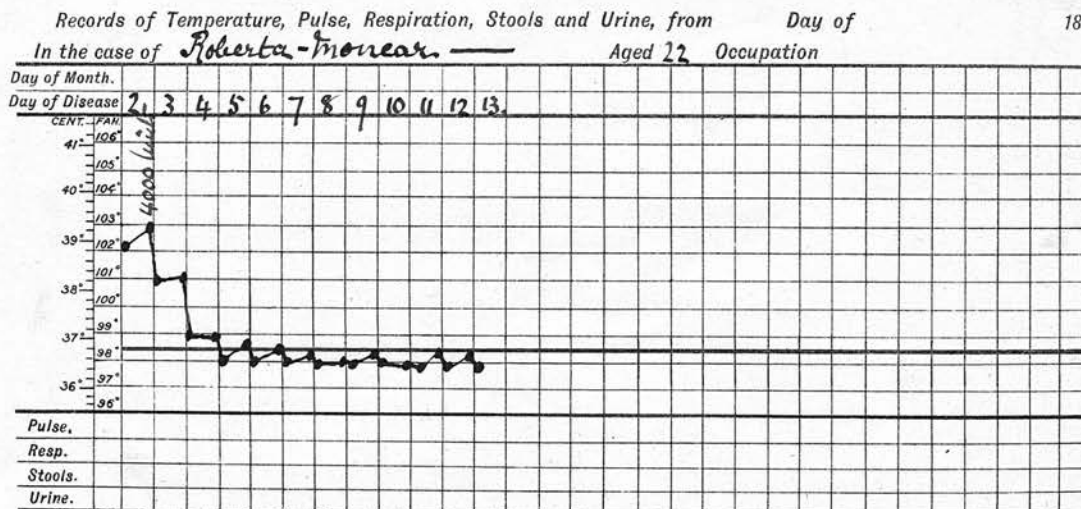
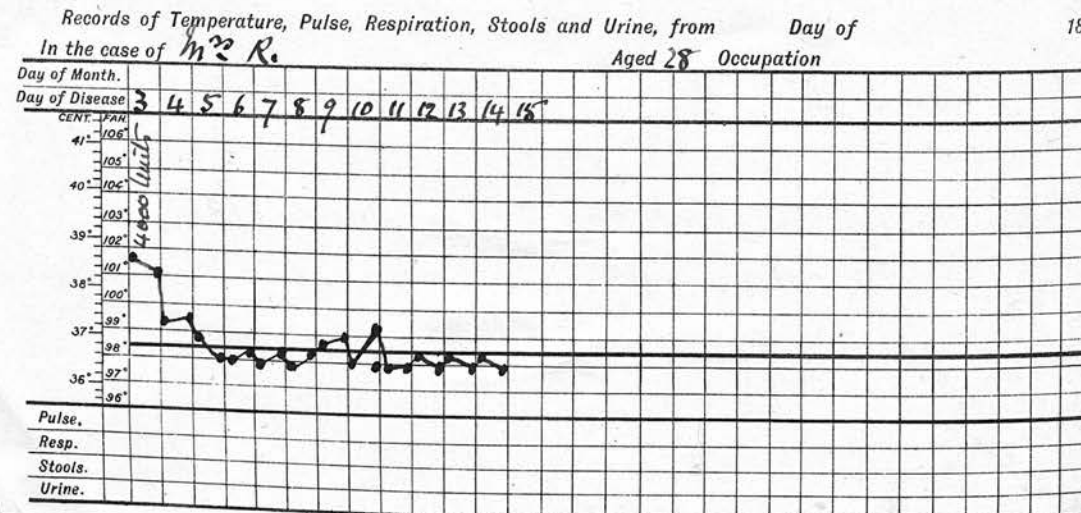


Chart 3

15



2. EFFECTS ON THE GENERAL CONDITION are chiefly denoted clinically by a rapid fall in the temperature, and a general improvement in the appearance of the patient.

The fall in the temperature is most conspicuous. Charts 1 - 5 show the fall in temperature when the antitoxine was given respectively on the 1st, 2nd, 3rd, 4th and 5th day of disease. After a fall more or less abrupt, the temperature will be seen to continue subnormal, so characteristic in uncomplicated diphtheria.

Chart 1 is that of a little patient, Rose T., aged 8, who was admitted to hospital with a mild throat condition which had the appearance of a sub-acute follicular tonsillitis. This soon cleared up under local treatment. After remaining in hospital some days, she complained of feeling unwell; was sick and vomited; temperature suddenly rose and the tonsils rapidly became covered with a thin membrane, in which numbers of Löffler's bacilli were found. Three thousand units were given on the evening of the first day. The temperature rapidly regained the normal. This patient made a rapid and uninterrupted recovery.

Charts 2, 3, 4 and 5 are those of cases which were/

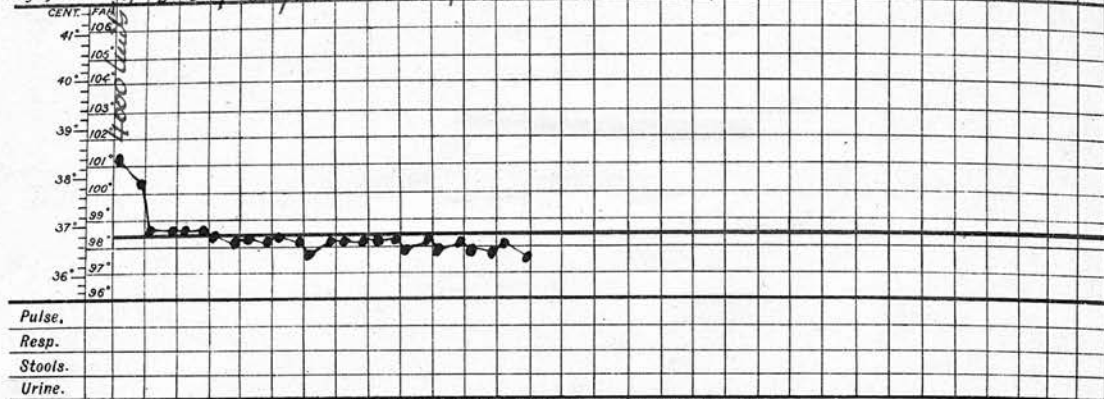
Chart 4

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of Pat 2. Aged Occupation

18

Day of Month.

Day of Disease 4 5 6 7 8 9 10 11 12 13 14 15 16



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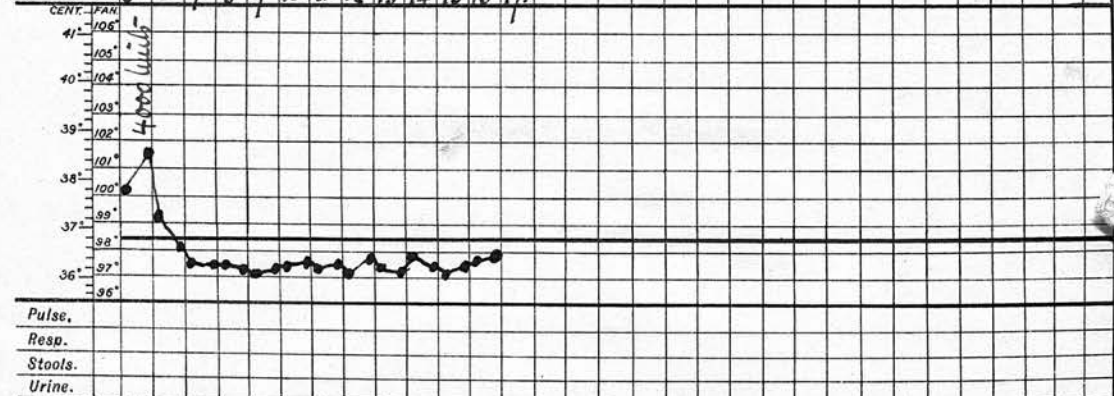
Chart 5

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of Alice B. Aged Occupation

18

Day of Month.

Day of Disease 5 6 7 8 9 10 11 12 13 14 15 16 17



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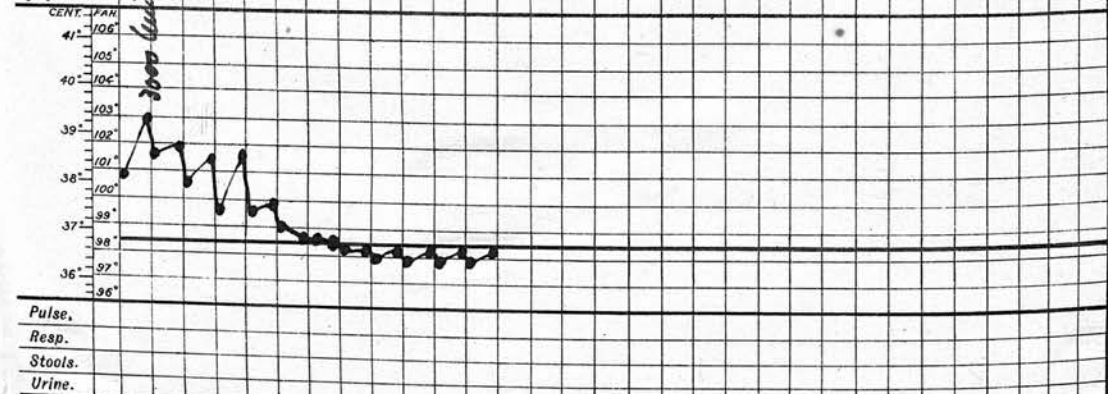
Chart 7

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of M. M. L. Aged Occupation

18

Day of Month.

Day of Disease



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were both clinically and bacteriologically diphtheria. They all show the same fall in temperature.

The fall in temperature is, however, always most characteristic in those cases where the antitoxine is given in large doses early in the disease. If the Klebbs-Löffler bacillus is associated with the streptococcus, or other progenic organisms, then the temperature remains up for a longer period. Charts 7, 8, 9 are those of three cases of septic tonsillitis, to whom antitoxine was administered as a safeguard. In none of these cases was there any evidence of diphtheria and in each, the temperature remained high until local applications improved the throat condition.

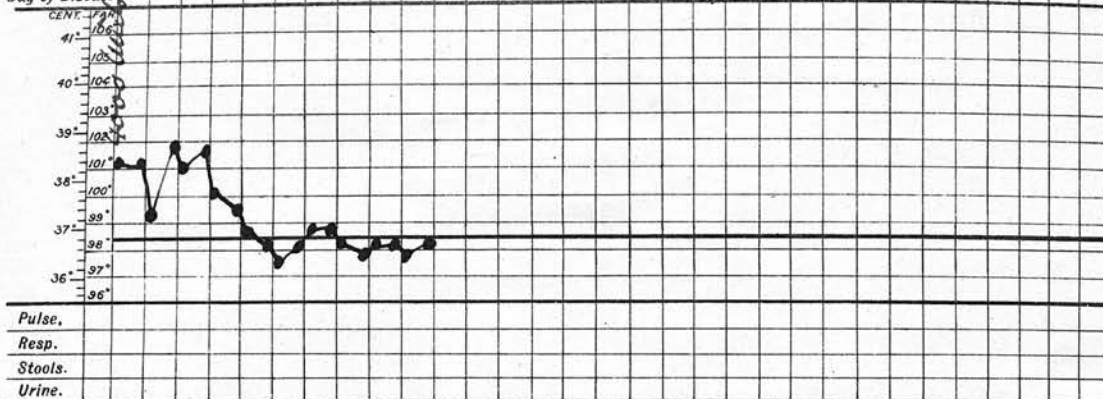
THE TIME OF ADMINISTRATION OF ANTITOXINE:

The entire success of the therapeutic application of antitoxine depends on its early administration. From the experimental point of view, a moment's thought on the principles which underlie the preparation, and standardisation of this drug, will show this must be true. In the process of standardisation a unit of antitoxine is proved to neutralise, or render inert, an equivalent of free toxine./

Chart 8

12

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of 18
In the case of *John D.* Aged Occupation
Day of Month.
Day of Disease

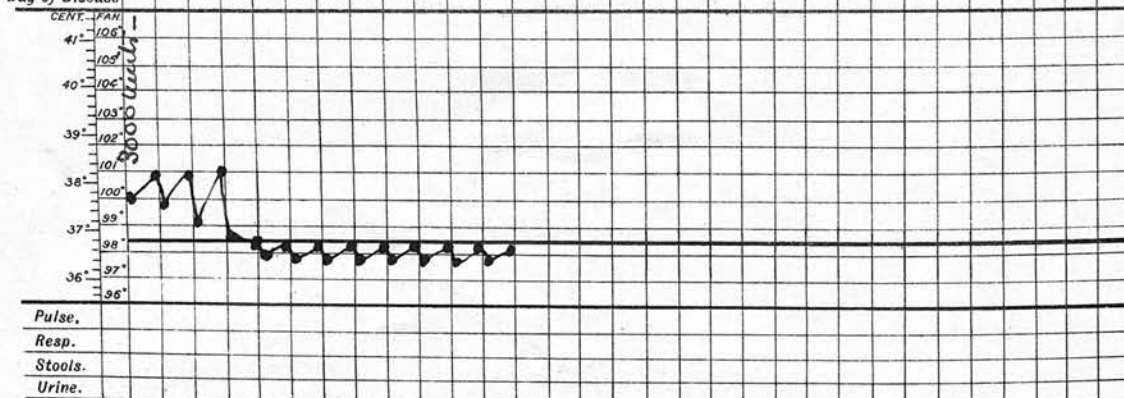


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Chart 9.

16

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of 18
In the case of *Robert D.* Aged 19. Occupation
Day of Month.
Day of Disease



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toxine. What the nature of the changes may be which the toxine undergoes when it enters the circulation and tissues of the body, is, I take it, not clearly understood. There is, however, abundant clinical evidence that it rapidly and injuriously affects certain tissues of the body, and as rapidly gets beyond the antagonising properties of antitoxine.

A grim warning is unconsciously implied in the close association of the antitoxines of diphtheria, and tetanus. For what do we find in practical medicine to be the results obtainable from these two drugs, both of which were announced at the one time, both discovered by experimental work conducted on parallel lines, and both proclaimed to be able "not only to protect animals against their respective diseases, but to cure them when already infected? In the case of the Diphtheria antitoxine when applied early, we have a most valuable means of treatment. The writer's experience of the anti-tetanic serum in six cases of tetanus treated while he was at the Royal Southern Hospital, Liverpool, was that the drug was of no use whatever. But why is it, that these two antitoxines theoretically of equal value, should in practical medicine yield such varying/

varying results? The one so satisfactory; the other so disappointing?

The reason appears to be that in the case of tetanus, by the time a diagnosis is possible, the toxine has become, as it were, so linked on to "the molecular constitution of the tissues that it has got beyond the scope of antitoxine. The same thing exactly occurs in diphtheria if the administration of antitoxine is delayed, for we shall see under "Heart Failure and Toxic Cases", have comparatively little good ~~the~~ antitoxine ~~does~~ in the later stages of this disease.

Statistics speak eloquently of the value of the early administration of antitoxine. Tables IV. and V. pp. 34 and 35 are copied from the Metropolitan Asylums Board's Report for 1896. It must first be explained that in Table V. all the cases were of a more severe type, and that during the year 1896, no less than 1,411 mild cases were admitted to the various hospitals from which the statistics were collected. These cases were not treated with antitoxine, and so are not included in Table V. Table IV., however, includes all cases. Moreover be it noted in Table V., no less than 48.6% of the cases were children under 5 years of age as against 31.1% included in Table IV. Again, of the cases in/

in Table V., 17.6% were laryngeal cases, whilst Table IV. only includes 1.9% of laryngeal cases. Thus a comparison of the two sets of cases is hardly fair, and puts antitoxine to a distinct disadvantage.

But let us compare the results. It may first be noted that in spite of the larger proportion of cases under five years of age, the death rate is reduced during this period from 47.4% in Table IV. to 32.2% in Table V., a difference of 15.2%. More interesting still is the comparison of the results with reference to the day of the disease, on which the case first came under treatment.

Of those treated with antitoxine, which came under observation on the first day of the illness, only 5.2% died, as against 22.5% treated in the former year without antitoxine. After the "1st day", the difference in the per cent. mortality gradually decreases until on the "5th day or later", the per cent. mortality is greater in cases treated with antitoxine.

T A B L E IV.

ALL CASES of DIPHTHERIA, before USE of ANTITOXIN, 1894.

(Day of Disease = day of disease on which patient was admitted to Hospital).

Day of Disease	1st		2nd		3rd		4th		5th & after		Total		Mortality per cent.
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	
Under 1	0	0	10	7	4	1	11	6	15	11	40	25	62.5
1 to 2	10	5	42	29	47	25	39	25	66	42	204	126	61.7
2 to 3	16	7	55	27	51	22	44	26	91	50	257	132	51.3
3 to 4	17	6	58	26	70	37	71	37	126	55	342	161	47.0
4 to 5	15	4	51	18	71	26	47	14	144	50	328	112	34.1
5 to 10	53	6	179	34	215	71	208	60	420	109	1075	280	26.0
10 to 15	12	2	85	4	79	8	59	5	128	22	363	41	11.2
15 to 20	6	0	23	0	33	1	28	0	70	6	160	7	4.3
20 and upwards	4	0	36	1	82	1	59	6	92	10	273	18	6.5
Total	133	30	539	146	652	192	566	179	1152	355	3042	902	29.6
Mortality per cent.		22.5		27.0		29.4		31.6		30.8		29.6	

T A B L E V.

CASES treated with ANTITOXIN, 1896.

(Showing day of disease on which the treatment was commenced).

Day of Disease.	1st		2nd		3rd		4th		5th & after		Total		Mortality per cent.
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	
Ages.													
Under 1	2	0	10	6	13	3	10	2	28	16	63	27	42.8
1 to 2	2	0	35	16	41	16	37	21	75	30	190	83	43.6
2 to 3	7	2	39	8	60	18	56	20	130	50	292	98	33.5
3 to 4	7	0	61	8	83	20	74	20	155	68	380	116	30.5
4 to 5	5	0	61	6	77	17	88	30	190	57	421	110	26.1
5 to 10	27	1	157	16	212	44	232	55	428	122	1056	238	22.5
10 to 15	7	0	33	1	47	3	53	12	113	20	253	36	14.2
15 to 20	0	0	3	0	8	1	6	1	21	4	38	6	15.7
20 and upwards	0	0	7	0	16	0	23	0	25	3	71	3	4.2
Total	57	3	406	61	557	122	579	161	1165	370	2764	717	25.9
Mortality per cent.		5.2		15.0		21.9		27.8		31.7		25.9	

It is obviously difficult to quote cases illustrative of the benefit of the early administration of antitoxine. To illustrate the converse is simpler, as will be done later. However, statistics show the death rate is reduced in much greater proportion in the cases treated early, than in those coming under treatment later. Clinical observations show

1. That the throat condition improves more rapidly.
2. There is less tendency to post diphtheritic depression.
3. That the tendency to irregularity of the pulse, and to heart failure, is greatly reduced.
4. That convalescence is more rapid, and less liable to complications and sequelae.

Under the heading of "Laryngeal Diphtheria", cases will be recorded to show that the early administration, in all probability, not only prevented a fatal termination, but obviated the necessity for surgical interference, that is, in other words, arrested the progress of the disease in a marked manner.

T A B L E VI.

ALL LARYNGEAL CASES, HOWEVER TREATED.

Ages.	1894			1896 (Antitoxin Year)		
	Cases	Deaths	Mortality per cent.	Cases	Deaths	Mortality per cent.
Under 1	9	8	88.8	13	8	61.5
1 to 2	66	52	78.7	61	31	50.8
2 to 3	85	55	64.7	92	30	32.6
3 to 4	79	49	62.0	117	26	22.2
4 to 5	76	43	56.5	90	22	24.4
5 to 10	138	72	52.1	131	32	24.4
10 to 15	3	1	33.3	11	4	36.3
15 and upwards	10	9	90.0	1	0	0.0
Total	466	289	62.0	516	153	29.6

VI. ANTITOXINE IN THE TREATMENT OF LARYNGEAL DIPHTHERIA.

The results which have followed the treatment of laryngeal diphtheria by antitoxine have been:-

1. To reduce the total death rate.
2. To reduce the number of cases in which laryngeal symptoms supervene, or in other words, to reduce the number of cases in which the membrane spreads from the pharynx to the larynx, after coming under treatment.
3. To minimise the necessity for operative interference.
4. To modify the method of operative interference.
5. To very considerably improve the chance of successful operation in cases in which such is imperative.

1. THE REDUCTION OF THE TOTAL DEATH RATE.

Table VI., opposite shows to a remarkable degree the reduction of the total death rate in the hospitals of the Metropolitan Asylums' Board.

Here it will be noticed the mortality of all laryngeal cases fell from 62% in 1894 to 29.6% in 1896, a difference of 32.4%. My own series of cases included 10 cases of a severe laryngeal type and of these three died. The following are the notes on the fatal cases.

Case 2/

CASE 2. - Laryngeal Diphtheria - Death.

Nellie M. aged 5, admitted to City Hospital, 3rd July, 1900.

The history was briefly this;- that three days previously, she appeared ill and complained of a sore throat. Had gradually got worse. The doctor was not called in until day of admission. He at once ordered patient to hospital.

3rd July. On admission, the patient was evidently seriously ill. The breathing was harsh and noisy. The face was pale and anxious looking, the pulse rapid, weak and irregular. There was indrawing of the lower costal cartilages, but this was not excessive. Eight thousand units of antitoxine were administered.

4th July. The patient passed the earlier part of the night fairly well, but in the morning the breathing became much worse and the pulse and appearance of the patient signified a serious collapse.

An intubation tube was introduced, but was shortly afterwards expelled and with it an almost complete membranous cast of the larynx and trachea.

Albumen is present in the urine in a most exceptional amount.

5th July. The patient's general condition is much worse. The intubation has failed to give relief. Tracheotomy was therefore decided upon as an only chance. For a little, this appeared to give marked relief, but about an hour and a half after operation, the child gave a sudden start and suddenly died of heart failure.

At the post mortem very little membrane was to be found in the upper part of the larynx. Lower down in the trachea, membrane was still adherent in patches, but no regular ring. The cause of death, however, was found to be in all probability due to the broncho-pneumonia of the right lower lobe, discovered post mortem.

CASE 3. - Laryngeal Diphtheria - Death.

Lena S., aged 4, admitted 7th July, 1900.

History. Mother states the child was feverish, and did not look well on the 5th. Next day, the child was croupy and hoarse; this became worse and to-day, 7th, the doctor was called in, and immediately sent the child to hospital. On admission, the child was seen to be in a very critical condition. The face was pale, and the lips somewhat bluish. There was pronounced inspiratory obstruction with great/

great stridor, indrawing of the lower costal cartilages. Intubation was at once resorted to, but without success. The child became cyanosed and died in spite of all attempts at resuscitation. No post mortem was obtained, but it is highly probable the intubation tube pushed a piece of membrane in front of it, and so occluded the air passage entirely.

CASE 4. - Diphtheria Laryngeal? Broncho-pneumonia -
Death.

Francis Russell, 14 months.

Admitted 17th June, 1900.

History. Has been treated for sore throat for a week. The day before admission patient coughed up a large piece of thick membrane, which the doctor pronounced to be diphtheritic and sent the patient to hospital. For three days there has been a purulent discharge from the nose.

On admission the child was extremely ill. The face was pale and the child very restless. The pulse was rapid, (144), weak and irregular. The respiration (40) noisy, and somewhat obstructed. There was slight indrawing of the lower costal cartilages. Examination of the throat was imperfect owing to the condition of the child, but no membrane could/

could be detected. A swab from the throat showed Löffler's bacillus to be present. Examination of the chest is difficult. No definite dulness could be made out, but bronchial wheezing is general; 6000 units of antitoxine were administered.

18th June. The breathing is more rapid, likewise the pulse, and the child is looking much worse.

19th June. Child died after repeated signs of collapse and heart failure.

At the post mortem, extensive patches of broncho-pneumonia were found scattered throughout both lower lobes. The left side of the heart showed acute endocarditis. There was no sign of membrane in the pharynx, larynx or trachea.

CASE 5. - Laryngeal Diphtheria.

This case is not included in the series under observation as it was not admitted to hospital. The history is, however, interesting and the case suggestive. The case was one for which the City Ambulance was sent, but returned with a note from the nurse in charge to say the case was too ill to lift, would I call and see it? On hurrying to the house, I found a well conditioned, healthy looking child, practically dying. The trachea was at once opened, but too late. The history was interesting.

Two/

Two days previously the child had been quite lively. The same evening he "caught cold". Next day was croupy and towards evening the doctor was sent for, who said the child had diphtheria and must be sent to the hospital. He notified the case, but as it was after hours, (that is, after 5 o'clock), it was not until next day that the case was sent for.

Cases 2 and 4 illustrate with what marked rapidity excessive obstruction may supervene. In neither, under existing conditions, was any treatment possible. Neither received antitoxine.

Cases 1 and 3 were both complicated and beyond treatment.

2. REDUCTION OF THE NUMBER OF CASES in which the membrane spreads from the pharynx to larynx after the administration of antitoxine.

In none of my own cases did this happen, nor have I seen it occur. I must again turn to statistics. Table 7. speaks for itself.

TABLE 7.

Showing frequency of Laryngeal Symptoms subsequent to admission to M.A.B. Hospitals.

		Antitoxine	
		1894	1895
			1896
Cases	3,042	2,965	3,300
Cases in which laryngeal symptoms supervened.	116	18	16
Percentage	3.8	0.6	0.48

3. DIMINUTION IN THE NUMBER OF CASES in which
operative interference is necessary.

It is in this class of cases that the results of antitoxine are seen to greatest advantage. Here, not only the efficacy of antitoxine can be clinically demonstrated, but the great advantage of early administration can be clearly proved.

CASE 6. - Laryngeal Diphtheria - Recovery.

Robert J., age, $2\frac{1}{2}$ years.

Admitted to City Hospital, 27th July, 1900.

History. On the 24th, it was thought the child had a bad cold. On the 26th, had a croupy cough, and "was breathing heavily".

On Admission. On the morning of the third day of illness, the child was somewhat restless. Had a croupy cough, was breathing noisily and there was considerable obstruction as indicated by marked indrawing of the lower costal cartilages. Six thousand units of antitoxine were administered on the morning of admission. Three thousand units more were administered early the following morning.

Examination of a film preparation showed presence of Löffler's bacillus.

27th. Child passed a very fair night. Is much quieter/

quieter on the whole. Breathing easier. Cough less troublesome, but still croupy. Pulse has kept good.

31st. Child has done very well. Obstruction has passed off. Child is quiet, sleeps well.

This case made a complete and uninterrupted recovery.

CASE 7. - Faucial and Laryngeal Diphtheria - anti-toxine - Recovery.

James M., 4 years.

Admitted to the City Hospital, 6th June, 1900.

History. Fell ill on the evening of the 3rd. Felt a little better on the 4th. Worse on the 5th, when the doctor first saw him and sent him to hospital. On admission, the throat was very dirty. A thick, grey membrane covered tonsils, uvula, and soft palate. Respiration is harsh and strident, and the cough is croupy. There is slight obstruction with indrawing of the lower costal cartilages. Breathing and obstruction became worse during first day in hospital.

Four thousand units of antitoxine were administered on admission and 6000 more added during the evening. Second dose appears to have improved the breathing very greatly.

8th./

8th. Breathing very much improved. Cough is still very harsh, but the pulse is fairly good. There is a considerable amount of albumen in the urine.

11th. Patient has done very nicely. The breathing is easy, the throat quite clean, cough still irritable. Convalescence uninterrupted. On admission typical Löffler bacilli were found in the stained specimen

CASE 8. - Faucial and Laryngeal Diphtheria - Anti-toxine - Recovery.

Barbara S., 14 months.

Admitted to City Hospital, 4th May, 1900.

History. Mother says the child has not appeared well for about a week. Doctor was called in on the 2nd when the throat was all right. Throat symptoms appeared during the night and child became dyspnoeic. Doctor was called in and sent the child to hospital.

On admission the child was markedly pale and somewhat collapsed, with quick, soft pulse, inspiratory stridor and very marked epigastric indrawing. Locally, both tonsils and sides of the uvula are patched.

Four thousand units of antitoxine administered and steam allowed to play about the head of the bed.

5th./

5th. Has had a good night. Some colour returned to the cheeks. Marked "croupy" cough, especially when being fed, but breathing is markedly improved, slight epigastric indrawing still persisting.

Occasional attacks of dyspnoea which soon passed off, occurred during the night.

8th. Continues to do very well. No membrane to be seen on the tonsils. Breathing quietly.

12th. Spotted erythema on face, otherwise well.

This child made an excellent convalescence and picked up rapidly.

CASE 9. - Laryngeal Diphtheria - Antitoxine -
Recovery.

John C., age 4, was recently seen by me in private. The history given by the mother was that the previous day the child appeared quite well in the morning. In the evening, he appeared drowsy, complained of headache, and the mother thought he had caught a cold. During the night, it was noticed his breathing was heavy and his cough croupy. This became worse. Next day, when I first saw him, the child had considerable obstruction. His breathing was noisy and his cough and cry very "croupy". There was a small patch on one tonsil. His temperature/

ture was 102. I immediately sent the case to the City Hospital.

For the notes on the subsequent treatment and progress of the case, I am indebted to Dr Ker.

On admission the child was very "croupy" and had considerable obstructive stridor. Six thousand units were administered and steam turned on. Next day, when I visited the child, he was wonderfully improved. Breathing was harsh with same inspiratory stridor, but much easier. He is now making a satisfactory convalescence.

Many more such cases might be quoted, as they are very common. The above will, however, serve the purpose. In each, the diagnosis appeared to be beyond doubt. In each, the obstruction, although marked, was not of long duration, and all showed marked improvement within 24 hours of the administration of antitoxine. Thus in any given case of moderately severe laryngeal diphtheria, the question must be decided whether operative interference is at once called for, or whether delay may be justifiable in order to see the effects of antitoxine. This is often a very difficult question to decide, for it must be borne in mind, that the success of operation/

operation depends very largely on its early performance.

An answer to the following considerations must decide the question.

- (a) What is the general appearance of the patient and the condition of the pulse?
- (b) How long has the patient been ill?
- (c) Is the obstruction very great?
- (d) Is the obstruction rapidly becoming worse?
- (e) What length of time must elapse before you can expect antitoxine to have the effect of checking the progress of the obstruction.

The absorption and therapeutic action of the antitoxine is known to be rapid. Ehrlich⁹ is said to have injected antitoxine in to the subcutaneous tissue of a child. Shortly afterwards, he withdrew a little blood from a vein; the serum of this he found to have considerable antitoxic properties.

Time must elapse, however, before the clinical manifestations of improvement in the patient's condition are evident. In the majority of cases, at least eight hours must elapse before there is any sign that the progress of the disease is being arrested; of course, a longer period must elapse, from 12 to 24 hours, before any decided improvement takes place.

4. MODIFICATION OF THE METHOD OF OPERATIVE INTERFERENCE.

Two methods of operative interference are available in laryngeal diphtheria, viz., tracheotomy and Intubation.

Tracheotomy is much the older operation. Its introduction dates back to the time of Bretonneau. It is the operation which has had by far the more extended trial.

Intubation was first introduced and practised by Bouchut of Paris in 1858. The difficulties and failures attending its early employment soon threw it into disfavour and disuse. It was not until 1885, when O'Dwyer, an American physician, announced a new set of tubes and apparatus for their application, that this method became well known. The introduction of antitoxine, however, was soon to put it on a sure and certain footing in practical medicine. It is not within the scope of these remarks to discuss the merits and demerits of these two operative procedures. Suffice it to say, that each has its own sphere of usefulness, that neither can entirely replace the other. Not only, however, has the introduction of Antitoxine markedly enhanced the/

the value of both these aids to treatment, but it has entirely changed the respective value attached to these two operations as a means of relief in laryngeal diphtheria.

Until of recent years, tracheotomy was the only operation widely advocated. Antitoxine has, however, altered these views and is now giving to intubation, the position of the operation of preference, tracheotomy becoming more and more, the operation of necessity. And why should this be so? We have already seen that an increasingly large number of cases of diphtheria subside under large doses of antitoxine, administered early, without any operative interference becoming necessary. Let us now go one step further, and we meet a set of cases a little more severe. In these, the appearance of the patient and the condition of the pulse is not so satisfactory; the obstruction appears to be too great to allow of any delay, and yet all we want is a little time, 12, 24 or 36 hours, when antitoxine will have done its work. These are the cases for which intubation is specially suitable.

CASE 10. - Laryngeal Diphtheria - Antitoxine Intubation - Recovery.

George C., age 7, admitted to City Hospital,
7th April, 1900.

History/



History. Mother states patient was playing about yesterday though she thinks he had a cold. This morning, throat became sore and he refused his breakfast. Doctor was sent for, who at once ordered him to hospital.

On admission, during the afternoon, there was considerable cyanosis, respiratory stridor, indrawing of the lower part of the chest wall and a very croupy cough. His pulse was rapid, 136, and soft, and his temperature 102.

Six thousand units of antitoxine were administered and intubation at once successfully performed. The breathing immediately became markedly relieved; the colour improved and the child became much quieter.

April 8th. Has had a good night, the respiration being quiet, except after coughing, which is set up on taking food. Pulse still rapid, but stronger.

9th. Four thousand units of antitoxine given. Child still improving.

10th. Pulse stronger and somewhat less rapid. Tube removed this morning.

11th. No return of dyspnoea. Erythematous antitoxine rash on the face, otherwise, doing well.

17th. Has made a good recovery. There is now only very slight cough at times. Convalescence complete and uninterrupted.

CASE 11. - Laryngeal Diphtheria - Antitoxine -
Intubation - Recovery.

I am indebted to Dr Ker for the notes on the following case.

Louisa F., aged 18 months, admitted to City Hospital, 7th October, 1900.

History. Patient took ill on the 5th. Was thought to have caught cold.

6th. Very restless, sick and vomiting, breathing laboured.

7th. Became much worse; doctor sent for, who sent her into hospital at once.

On admission child was in great distress, there being very marked indrawing with crowing respiration; 6000 units antitoxine administered after admission and the child intubated at once. Latter gave great relief.

8th. Child coughed up a piece of thick pearly white membrane, examination of which revealed presence of Löffler's bacillus. As the child was unable to swallow properly, tube was removed, but had to be re-introduced.

Tube finally removed on the morning of the third day after introduction. This child made a perfect recovery.

CASE 12. - Laryngeal Diphtheria - Antitoxine -
Intubation? - Recovery.

Annie Scott, Age 3.

Admitted 17th September, 1901.

History. Patient is said to have been ill for three days.

Has been croupy for two nights, and is gradually becoming much worse.

On admission. Patient looked very ill. Breathing is loud, noisy and difficult. There is a barking cough. There is considerable indrawing of the lower costal cartilages.

There is a grey membrane on both tonsils. Swab reveals very numerous Löffler's bacilli.

Ten thousand units of antitoxine administered about mid-day. Breathing became much worse during the afternoon; 6000 more units administered at 6 p.m. About 10 p.m., it was thought safest to intubate. This was done. Tube immediately coughed up a complete cast of larynx and trachea. Child very much better afterwards. Had only one spasm of difficult breathing about 4 a.m.

Six thousand units more antitoxine were given.

18th. Breathing very much better. Patient swallows well; 6000 more units given to-day at 3 p.m., and repeated again at 11 p.m. In all, this child aged 3, has had 34,000 units in two days.

20th. Breathing still a little noisy, otherwise very well. No sign of any actual obstruction.

This patient made a good recovery. There was no rash, no albuminuria, no complications.

Antitoxine has therefore, not only diminished the necessity for operative interference, but has also minimised its severity. Previously, intubation failed because the tube had to remain in the larynx too long. Under present treatment, the duration of the obstruction has been greatly shortened; and intubation which is undoubtedly the less severe operation is capable of tiding over the crisis of obstruction in a large majority of cases. Should it fail, resort may be had to tracheotomy without prejudice to that operation.

5. IMPROVEMENT IN THE RESULTS OF OPERATIVE INTER-FERENCE since the introduction of antitoxine.

Here, the results obtained from Tracheotomy, previous to, and following the introduction of antitoxine, will alone be considered.

This course is adopted in the first place, because Intubation was not widely practised before the introduction of antitoxine and so reliable statistics are difficult, or impossible to obtain; in/

in the second place, because so far the operation of Intubation has been practised by experts alone, and to this reason the improved results might be attributed. In the case of tracheotomy, this cannot be said. It is the older operation and its technique was quite familiar in all details long before the introduction of antitoxine, nor did this event alter it in any way. Moreover, tracheotomy is the more serious operation of the two, and thus puts antitoxine to a more severe test.

Table VII. and VIII. on pp. 57 and 58 speak for themselves.

Could anything more convincing be asked for, than the fact that is implied in these tables, namely, that the mortality following so serious an operation as tracheotomy in laryngeal diphtheria, has been reduced to a figure much lower than that which denoted the mortality from all laryngeal cases, and very little higher than that, which has from time to time, been brought forward as the total per cent. mortality of all cases of diphtheria previous to the introduction of antitoxine.

TABLE VII.

Case Mortality of Tracheotomy in children under 5
years of age at Guy's Hospital.

NON-ANTITOXINE.

Date	Cases	Deaths	Mortality %
1887	20	16	80
1888	14	8	57.1
1889	16	15	93.7
1890	18	14	77.7
1891	15	9	60
1892	22	19	86.3
1893	22	15	68.1
1894	19	16	84.2
Total 146		112	76.6

ANTITOXINE.

Date	Cases	Deaths	Mortality %
1895	10	2	20
1896	21	8	38.09
1897	8	1	12.5
Total 39		11	28.2

T A B L E ~~VIII~~ (13).
All Tracheotomies.

Ages.	1894.			1896 (Antitoxin Year).		
	Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
Under 1	5	4	80.0	2	2	100.0
1 to 2	33	29	87.8	32	21	65.6
2 to 3	46	35	76.0	42	18	42.8
3 to 4	53	33	62.2	40	15	37.5
4 to 5	45	32	71.1	36	11	30.5
5 to 10	75	47	62.6	56	17	30.3
10 to 15	1	1	100.0	4	3	75.0
15 and upwards	3	3	100.0	0	0	0.0
Total.....	261	184	70.4	212	87	41.0

VII. ANTITOXINE IN THE TREATMENT OF "TOXIC CASES"
AND "HEART FAILURE" IN DIPHTHERIA.

In this class of cases are included those which come under observation at a later stage of the disease, or those which, owing to some personal idiosyncrasy of the patient, or special virulence of the bacillus, have become profoundly affected by the diphtheritic toxine.

Such cases are readily recognised. The face is pale, and has a peculiar waxy appearance. There is a frightened, apprehensive look about the eyes. The child is restless, and there is frequently a sighing respiration. The pulse is usually rapid, but may be dangerously slow. It is always small and soft, with a marked tendency to become irregular, and intermittent. The pulse in such cases may vary considerably during the day, or from hour to hour; at one time showing all the characters of collapse, an hour later recovering a more steady character.

Such cases are at any moment liable to sudden, fatal heart failure. What then is the position of antitoxine in the treatment of such cases? All that antitoxine can be expected to do here is to check the local condition, and neutralise any free toxine/

toxine that may be circulating in the blood; to, as it were, destroy the "brewery" from which the fatal intoxicant is derived. More than this, it cannot do; the damage to the neuro-muscular system of the heart has been done, and no amount of anti-toxine will undo it. If sufficient time is allowed, it will clear up the throat or local condition. The ultimate recovery, however, will depend on the constitution of the patient, the severity of the poisoning, the benefit derived from such drugs as Alcohol and Strychnine and judicious dieting.

CASE 13. - Toxic Case - Heart Failure - Death.

Bella P., aged 6, admitted 31st September, 1900.
History. Onset somewhat indefinite. Has been ill for at least six days.

On admission patient appeared very exhausted, face pale and pasty. Is very restless. Pulse 100, very small and irregular. Both tonsils are covered with a thick, dirty grey membrane. The breath is very offensive and there is ill smelling discharge from the nose. This child has a thoroughly poisoned appearance. Examination of a piece of membrane from the throat shows large numbers of Löffler's bacilli and streptococci.

1st/

1st August. Patient very restless and exhausted, almost pulseless at times. Is fed per rectum as food causes vomiting.

2nd. Patient quieter, but pulse shows no improvement. The vomiting has ceased and the throat condition is improved. The bleeding from the throat which occurred on two previous days has ceased.

3rd. Pulse still very bad. Patient sinking. Died suddenly same evening of heart failure.

There was abundant albumen in the urine since admission.

Six thousand units of antitoxine were given on admission and 6000 units repeated the next morning.

CASE 14. - "Toxic" - Death.

Katie M., aged $5\frac{1}{2}$ years.

Admitted 18th July, 1900.

History. Has felt ill for a week. Sickness and vomiting on the 15th. Mother noticed yesterday there was a bad smell from the child's mouth.

On admission, this case was at once seen to be of a severe "toxic" type. The child had a filled, toxic look. The face was pale, the child restless; the pulse was 120, soft, rapid and irregular. The whole of the back of the throat was covered with a thick/

thick, diphtheritic looking membrane. There is some stridor, but no obstruction; 6000 units of antitoxine were administered on admission.

19th. No improvement in general condition. Died suddenly of heart failure this morning.

CASE 15. - "Toxic" - Death.

David W., age 16.

Admitted 28th September, 1901.

History. Has been laid up for five days.

On admission patient was obviously very ill. He was pale and looked exhausted. Pulse somewhat rapid (104), soft and intermittent.

Both tonsils and the uvula are extensively covered with a thick, grey, diphtheritic looking membrane.

Ten thousand units antitoxine administered on admission.

29th. Throat somewhat improved. General condition no better. Six thousand units more antitoxine given.

5th Oct. Has been holding his own nicely. Slight palatal paralysis. Vomiting has started, which has rendered the pulse very weak.

7th. Vomiting still troublesome. Pulse irregular.

11th. Died suddenly this morning of heart failure.

DOSE OF ANTITOXINE IN "TOXIC" CASES.

All authorities appear agreed that very large doses should be administered to cases of this class. It is, in my opinion, just open to question whether this is quite wise. Of course, no case should be refused antitoxine and the dose should be fairly large. Thus a dose of 12,000 units will usually have a marked effect on the throat condition and perhaps no smaller dose should be administered. With regard to larger doses in these cases characterized by the great tendency to heart failure, some regard must be had for the amount of serum injected. It will be seen later than in the "rashes" and "pyrexia" which so often follow the administration of antitoxine, it is quite common for a pulse of 100 or 110 to suddenly shoot up to 130 or 140 or even to 160. It is doubtful if these attacks ever leave a pulse in ordinary cases, as good as it finds it; it would appear still more doubtful if the "Toxic Heart" can stand this extra strain. In such cases a highly concentrated serum is very necessary.

With regard to position of antitoxine to "Heart Failure" itself, it may be repeated that antitoxine is as it were, a prophylactic. If sufficient/

ficient antitoxine is given early, it will prevent in the large majority of cases, the occurrence of this dreaded clinical phenomenon. By neutralising the free circulating toxine, by neutralising the toxine at the site of infection and thus allowing the phagocytic action of the tissues to overcome the bacilli, it will antagonise the cause of subsequent heart failure and tend to prevent its onset, but that is all. When the toxine has done its work, no amount of antitoxine has, clinically, any beneficial effect on the damaged heart; on the contrary, the serum in which the antitoxine is contained, may have the reverse effect.

VIII. ANTITOXINE AND DIPHTHERITIC PARALYSIS.

Post diphtheritic paralysis may be looked upon as a later manifestation of the toxic effects of diphtheria.

The occurrence of paralysis appears to be more frequent of recent years. This is probably due to the fact that under the antitoxine treatment, a much greater proportion of severe cases survive the acute stages to be later attacked by paralysis. In the Metropolitan Asylums' Board Report the percentage of cases of paralysis rose from 13.2% in 1894 to 21.3% in 1896.

I have notes of only three cases of paralysis, which occurred in my own series. In all, paralysis of the palate was first observed. All cases were of more than average severity. All came under observation late, and in all albuminuria was present. In one case, the paralysis was noticed on the 21st day, in the other two on the 22nd day.

CASE 16. - Diphtheria - Paralysis - Discharged.

Alex. M., aged 20, admitted 5th June, 1900.

History. This is supposed to be about the 9th day of the disease. First complained of feverishness, sore/

sore throat and pain on swallowing.

On admission the throat looked typically diphtheritic. Both tonsils and the uvula were covered with a thick, grey, firm membrane.

Film preparation showed abundant Löffler and little else.

Five thousand units of antitoxine were given.

15th. This throat has been an obstinate one to clean. The tonsils are now free from membrane, but the uvula is still patched with membrane, which renews as soon as removed.

19th. Has a distinct nasal twang. Uvula not yet free from membrane. Pulse only fair.

23rd. Throat at last free from membrane. Palatal paralysis still marked.

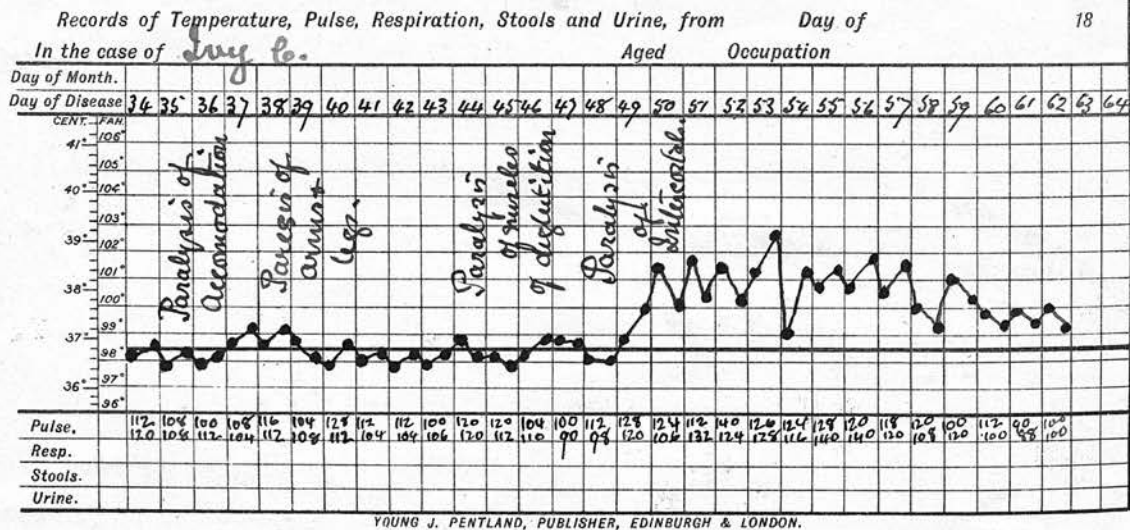
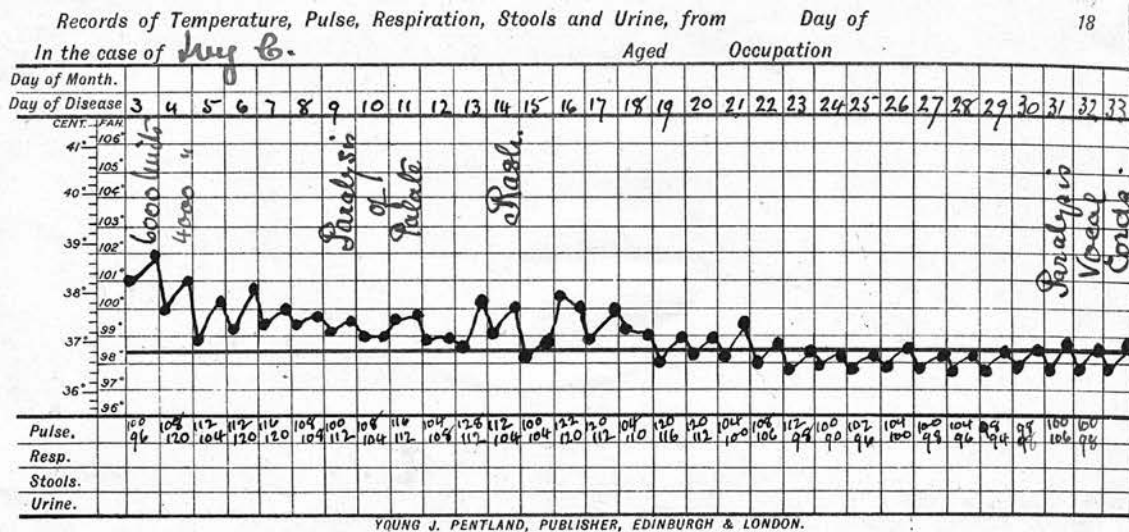
30th. Still somewhat shaky.

The lessons to be learned from this case are,

1. That the antitoxine was administered too late.
2. That the dose was insufficient.

I learned at a later date that this patient died some weeks after being discharged from hospital. It is evident from the story the parents tell that the paralysis extended considerably, and affected, at least, the legs and muscles of deglutition.

For/



For the notes on the next case which shows many points of interest, I am indebted to Dr Ker.

CASE 17. - Diphtheria - Paralysis - Tuberculosis - Death.

Ivy C., aged 18.

History. Is said to have been ill for three days. First complained of sickness, and vomiting, and a feeling that her throat was swollen.

On admission the patient was pale, and looked ill. Both tonsils were swollen and covered with membrane, which extended forward on to the soft palate and uvula. Löffler's bacilli present on examination. Six thousand units of antitoxine were administered. Next day, the throat condition had not improved so 4000 units more antitoxine were given.

On the 9th day of the disease, some palatal paralysis was noticed as evidenced by a distinct nasal twang.

On the 31st day of disease, the voice became very weak and the act of swallowing difficult. There is evidently some paralysis of the vocal cords and muscles of deglutition.

On the 31st day of disease, paralysis of accommodation was first noticed. This was followed two days later by weakness in the power of the arms/

arms and legs. Sensibility over the limbs, somewhat doubtful, if anything slightly impaired. Knee jerks absent.

44th day of disease. Paralysis of deglutition is now so marked as to render it unsafe to administer food except by enemata, and by the stomach tube, which latter the patient swallows well. Cycloplegia still persists.

On the 48th day of disease paralysis of the intercostal muscles made itself apparent. The patient was now in a helpless condition. She could move neither leg nor arm, was unable to feed herself and only able to whisper that she wanted to cough, but could not do so.

The bladder and rectum were unaffected. There being very little left unparalysed, convalescence commenced and progressed very slowly.

On the 98th day of disease, she started again to take food normally through the mouth. Her voice is stronger and articulation has improved. Can now move her arms and legs. It testifies eloquently to the nursing this case received, that she recovered without the suspicion of a pressure sore. After so far entering upon convalescence, it was very disappointing that this case should have contracted/

tracted acute tuberculosis from which she very soon died.

Instances of less severe cases might easily be quoted, but clinically, the cases in which paralysis usually appears, are those of "low toxic" type, which escape heart failure. They are usually cases which come under treatment somewhat late in the disease. From the experience of more severe cases of apparently the same type, it is safe to say that when the importance of the early administration of antitoxine in large doses is more widely appreciated, these cases will be less common than they are at present. Until such time, the occurrence of paralysis is sure to become more prevalent, due to the larger number of severe cases antitoxine saves from Heart Failure and Death in the earlier stages of the disease.

IX. ANTITOXINE IN RELATION TO ALBUMINURIA, ANURIA
AND NEPHRITIS.

There appears little doubt that since the introduction of antitoxine, the percentage of cases in which albuminuria appears is greatly increased.

In the Metropolitan Asylums' Board Report, the percentage rises from 24.1% in 1894 to 53.4% in 1896. Here again, it has been urged that the diminished mortality among severe cases, explains the fact to a certain degree. There is little doubt, that albuminuria is much more constant in the more severe cases. Again, it has been proved that among fatal cases, life has been prolonged by the use of antitoxine and the longer a severe toxic case lives, the more likely is albumen to appear in the urine. Apart from these causes, it is, however, not certain that the administration of large doses of serum does not, in a certain proportion of cases, aid the production of albuminuria.

With normal kidneys and under physiological conditions, the serum-albumen would be used in general metabolism of the tissues, and not excreted as such. But in such a condition as Diphtheria, where the kidneys are more or less affected by the diphtheritic/

diphtheritic toxine, it is quite possible the serum may aid in the production of albuminuria. The points of clinical importance, however, are

1. That the albumen present is generally small in amount.
2. That it is rarely associated with the presence of blood.
3. That the presence of albuminuria is transient, seldom lasting many days.
4. That it apparently leaves no ill effects behind.

The occurrence of Nephritis is rare in uncomplicated diphtheria, and from statistics, it would appear that this more serious condition has not increased in frequency since the introduction of Antitoxine.

ANURIA:

In the earlier statistics, reference to Anuria as a cause of death, following the administration of antitoxine, is not infrequent. Dr Lennox-Browne⁶ was particularly unfortunate. In eight of the first cases he treated with antitoxine, six died, with anuria as the most prominent symptom. It is quite probable that the earliest samples of antitoxine used in this country were responsible for some of the renal complications, for of late years/

years statistics are much more reassuring on this point. And it may be concluded that with the improved drug at present in use, antitoxine does not add to the danger of serious renal complications in diphtheria.

X. ILL EFFECTS FOLLOWING THE ADMINISTRATION OF
ANTITOXINE.

1. COLLAPSE.

Cases of fatal collapse following the administration of the antitoxic serum have been recorded. Dr James L. Taylor¹⁵ reports one from America. In this case, a preventive dose of Behring's serum was administered to an apparently healthy girl. She was dead five minutes later. Other cases are on record of sudden fatal collapse, but they are exceedingly rare. The explanation offered in some of the cases is that a vein was punctured and that the introduction of a large quantity of serum into the circulation was the cause of death. The records of the cases treated with antitoxine at the Edinburgh Fever Hospital, show no such cases, nor is such mentioned in the large number of cases included in the Metropolitan Asylums' Board's Report.

2. TOXIC SYMPTOMS arising shortly after injection
of serum.

Dr Goodall⁹ reports two cases of children aged 4 and 6, in whom the administration of antitoxine was rapidly followed by a rash and marked collapse. This was followed in one case by shivering and a rigor/

rigor and in the other by vomiting and cyanosis. Both cases recovered.

The case reported by F. Rauschenbusch and quoted by Dr Washbourne⁹ is of interest. "To five children were administered preventive doses of 200 units, from the same bottle of antitoxine, which contained 1000 units. No untoward results occurred to four of the children, but one aged 10, developed serious symptoms. Five minutes after injection, a marked eruption, attended by severe itching appeared at the site of injection and rapidly extended up the thigh and on the right side of the face. In ten minutes, the whole body was covered with a dark scarlatiniform eruption, and the patient fainted. After coming round, marked collapse continued; the pulse at the wrist could not be felt, and the heart beat was exceedingly weak. The eruption quickly disappeared except from the face. Two hours later, vomiting occurred, and the child improved. Eight hours later, the hands, feet and face were oedematous, and there was marked itching. Next morning, the child was better, and thenceforth gradually recovered. Two years previously the child had suffered from diphtheria, and was treated with 600 units/

units of antitoxine without ill effect."

3. SEPTIC TROUBLES at the site of injection need only be mentioned to be dismissed as inexcusable in these days of aseptic surgery. Only one such case has occurred at the Edinburgh Fever Hospital since the introduction of antitoxine into that Institution.

RASHES AND PYREXIA FOLLOWING THE ADMINISTRATION OF ANTITOXINE.

By far the most frequent occurrence of an unwelcome character following the administration of antitoxine, is the appearance of a rash.

The frequency of antitoxine rashes appears to vary considerably, some statistics showing 25%, others 35%. In my own series of cases, in 68 cases on which I have definite notes on the subject, rashes occurred in 40 or in practically 59%.

TIME OF ONSET AND DURATION OF THE RASHES.

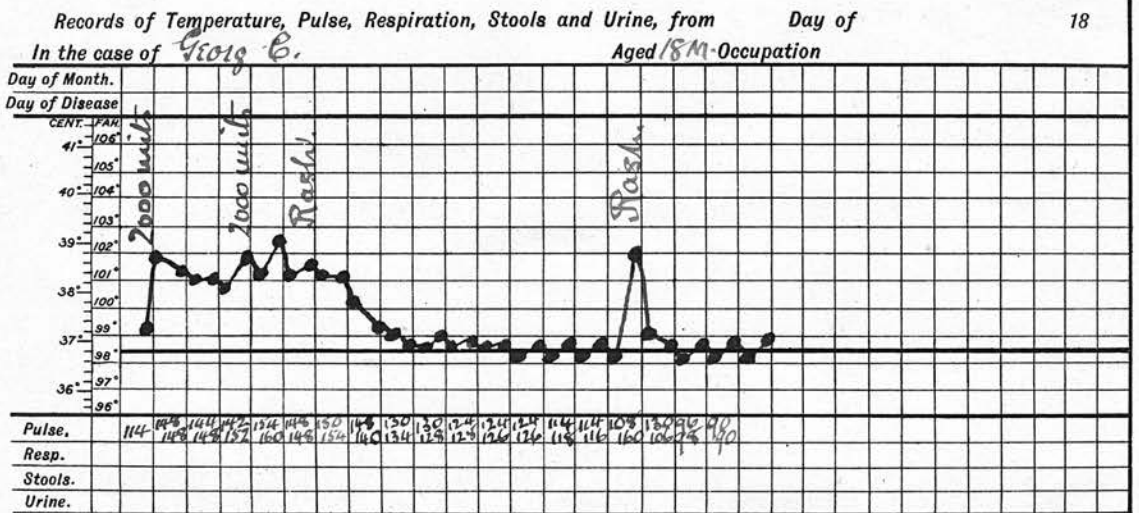
In a few apparently susceptible subjects, antitoxine rashes appear very shortly after the administration of the drug. In other cases the rash does not appear until weeks afterwards. The largest/

largest number of cases appear on the 8th, 9th and 12th days.

The duration of the rash is likewise very variable. The average length of time that one rash persisted in my own cases, was about $3\frac{1}{2}$ days, the shortest time being one day, the longest 8 days. In many of these cases, more than one rash appeared, with varying intervals between them. The fleeting character of these rashes makes it possible for milder cases to be overlooked, for such a rash may be quite distinct on the body at one time, and in an hour or two, it has quite disappeared. On the other hand, Washbourne⁹ states that the one rash may persist for three weeks.

APPEARANCE AND SITES OF ANTITOXINE RASHES

1. By far the most frequent antitoxine rash met with, is the more or less profuse, patchy, erythema. It is like nothing but a "toxic" rash. Its distribution is varied; as a rule, it appears on the extensor aspects of the arms and legs. It may be localised to one part, or if more severe may spread irregularly all over the body. If the erythema commences round the seat of injection, it may at first closely resemble erysipelas. It is in these cases that/



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that considerable confidence will be required in the thoroughness of the disinfection of the skin previous to injection. The rash will appear somewhat raised, be of a bright red colour, has a definite, but irregular outline. Together with a rise of temperature, and a rapid pulse, such a rash may give rise to no small amount of uneasiness for a little. Fortunately, these rashes are seldom sufficiently consistent, to remain long of the one character.

Chart 8 is that of a patient aged 18 months, who was admitted to the City Hospital on 2nd July, 1900.

On admission the throat presented a septic appearance. The tonsils were ragged, and covered with a thin membrane. The film preparation showed no definite evidence of diphtheria, but abundant stains of streptococci were present. Only a small dose of 2000 units was given on the day of admission, and repeated again three days later. Two days after this second dose, a red, raised erythema appeared round the site of injection, very like erysipelas. As the throat was a very septic one, it was thought it was erysipelas. However, the rash rapidly spread all over the back, and chest, with no further signs/

signs of the graver trouble. The character of the second rash denoted on the chart, was somewhat similar to the first, but appeared irregularly over the body.

2. The next most frequent type of rash is perhaps that of an urticarial character. Here again, the rash may be confined to the limbs and especially to the extensor aspects, and to the neighbourhood of the joints. It is as a rule mild, and not very extensive, but sometimes the urticaria may be most profuse covering the whole body. Occasionally, patients complain considerably from the discomfort of itching while the rash is out, but as a rule the discomfort is very trifling compared with the profuseness of the rash.

3. At other times, the rash makes its appearance as a scarlatiniform blush all over the body. It has not, as a rule, the typical punctate appearance of Scarlet, and if the rash is profuse, the face is quite likely to be affected. On the top of this scarlet like blush, other rashes resembling measles may appear or patches of erythema of larger size, and irregular distribution may supervene.

Chart/

Chart 9.

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of Anna S. Aged 9. Occupation

18

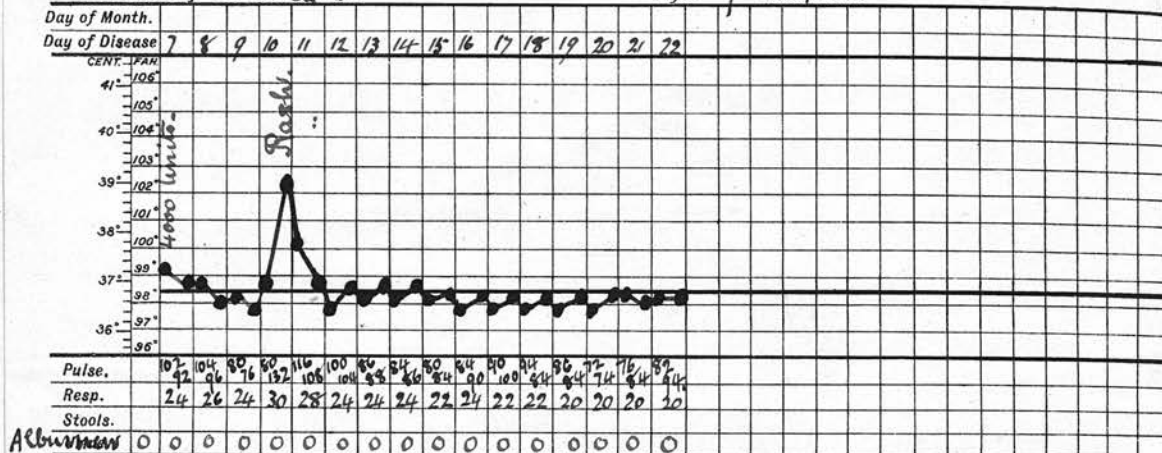


Chart 10

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of Madeline C. Aged 8. Occupation

18

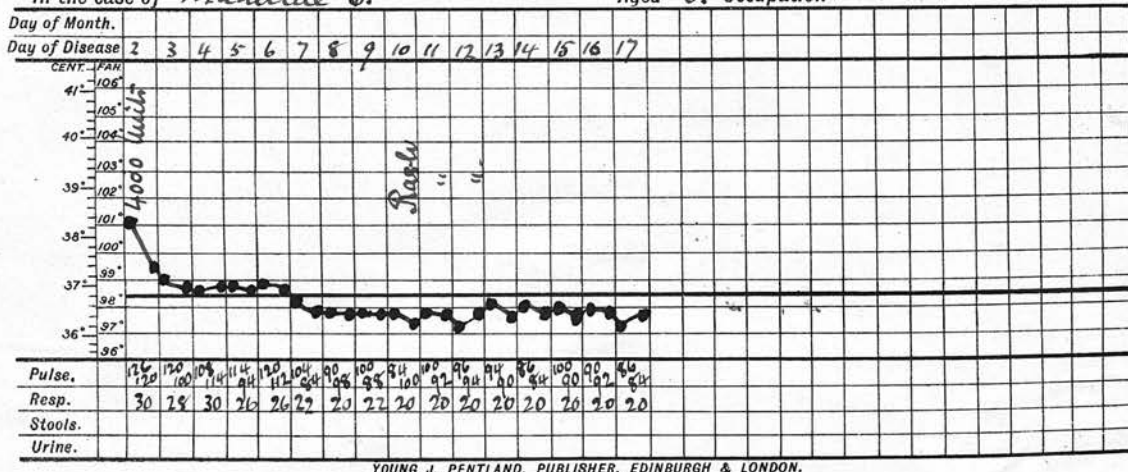


Chart 11.

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of Thomas C. Aged Occupation

18 19

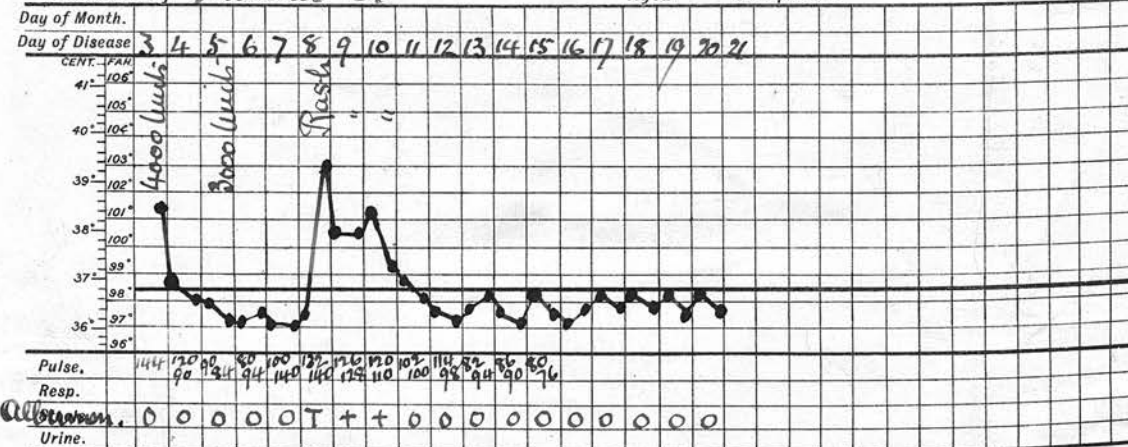


Chart 9 is that of a case in which the rash "uncomfortably resembled that of scarlet." It will be noticed the temperature suddenly shot up to 102 and that the pulse rate rose from 80 to 132.

4. Other rashes closely resemble measles or German measles. A specially typical case of such will be quoted later.

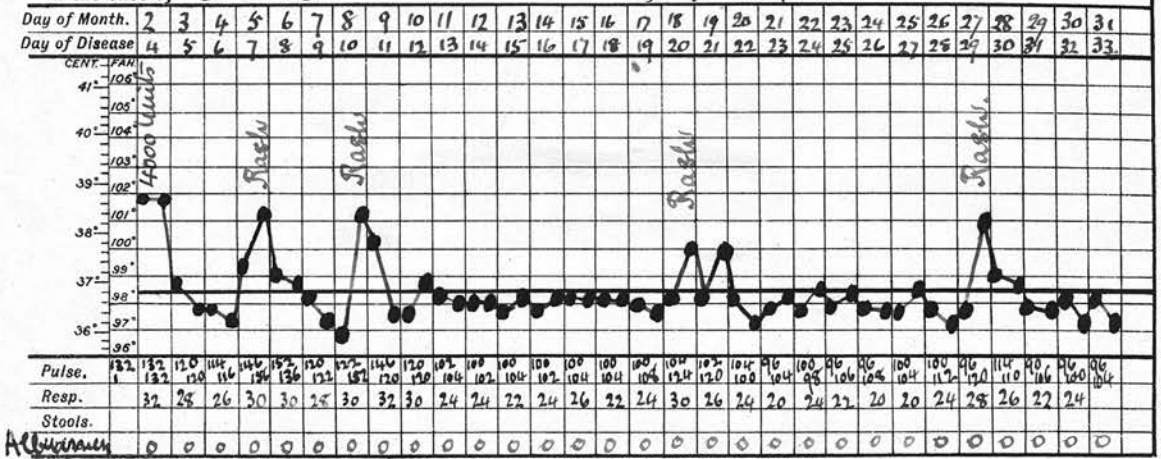
PYREXIA ASSOCIATED WITH ANTITOXINE RASHES.

In the great majority of cases, a variable amount of elevation of the temperature accompanies antitoxine rashes. As a general rule, the more profuse the rash, the higher the temperature rises, but sometimes most profuse rashes occur with no rise of temperature whatever. This is seen in Chart 10. In this case profuse patchy erythema covered abdomen, legs, arms and face.

Chart 11 shows a somewhat sharp reaction both as regards the rise in temperature and the increased pulse rate. It is interesting to note the fleeting albuminuria in this case during the time the temperature was elevated.

Chart 12 shows the occurrence of four distinct rashes, with in each practically the same elevation of/
of/

Records of Temperature, Pulse, Respiration, Stools and Urine, from 2nd Day of July 1890
In the case of Ella B- Aged 3 Occupation



of temperature. The first rash appeared three days, and the last 25 days after the injection of anti-toxine.

With reference to the treatment of these rashes, little, if anything, is as a rule, necessary. Professor A. E. Wright²⁰ of Netley advocates the use of Calcium Chloride whether, or not, the rash be associated with diminished coaguability of the blood. It is difficult, however, to see how the results of any treatment can be estimated in a condition which varies so considerably in different cases and in the same case from day to day.

DIFFICULTIES IN DIAGNOSIS OF ANTITOXINE RASHES.

In many cases the recognition of these rashes is a matter of considerable difficulty. The knowledge that diphtheria does not protect against any of the other infectious diseases and that Scarlet Fever and Diphtheria very frequently occur together in the same patient, only increases the difficulty.

In the case of Fever Hospitals, a moment's thought of the serious consequences which may follow the introduction of other infectious diseases among children suffering, or convalescing from diphtheria, will show that these rashes are apt to cause uneasiness to the medical attendants.

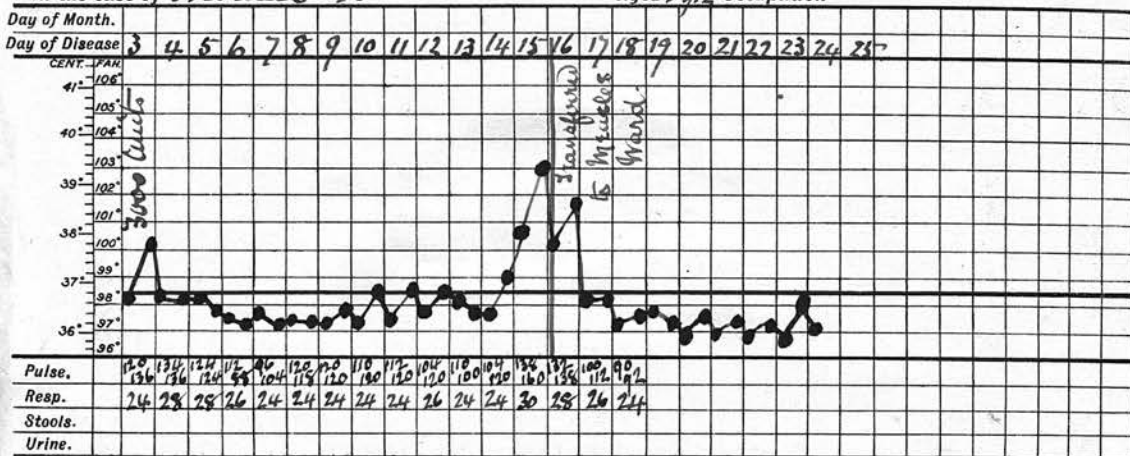
Mistakes/

Chart 16.

19

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of Thomas T. Aged 1 1/2 Occupation

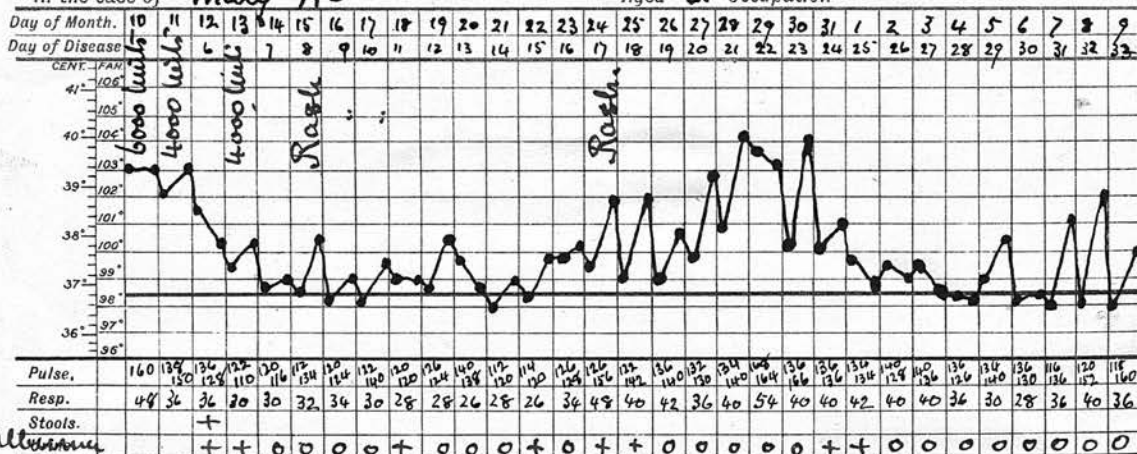
18



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Chart 17

Records of Temperature, Pulse, Respiration, Stools and Urine, from 10th Day of January 18
In the case of Mary Jr. Aged 3. Occupation



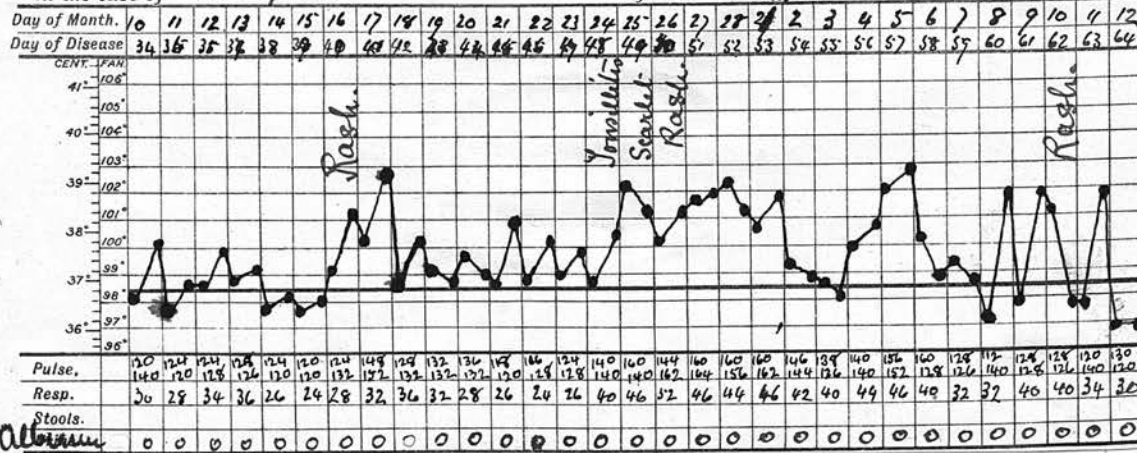
all

Chart 17.

21

Records of Temperature, Pulse, Respiration, Stools and Urine, from Day of
In the case of Mary Jr. Aged 3. Occupation

18



all

Mistakes may arise in two ways.

1. Antitoxine rashes may be diagnosed as those of other fevers.
2. Other fevers may be incubating and later the rash may be diagnosed as antitoxine rash.

I am indebted to Dr Ker for the next two cases.

Chart 16. This is the chart of a case where the former mistake was made. The red line down the chart denotes the time the case was transferred to the Measles wards. At that time, it will be noticed the temperature was 103 and the pulse had increased to 160. The rash is said to have closely resembled that of measles and the child had cough and "had sneezed". Possibly it was the information obtained from the parents that there was measles on the same stair, that caused the error. However, the temperature chart and behaviour of the rash very soon showed it was an antitoxine rash.

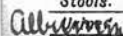
Chart 17. This was a most perplexing case. On admission the patient was suffering from severe laryngeal diphtheria for which tracheotomy was found necessary. Fourteen thousand units of antitoxine were administered. Five days after admission, the first rash appeared. This was a profuse urticaria which worried the child very considerably. Nine days later/

later a second rash appeared which closely resembled that of measles. Twenty-three days later, a third rash appeared and nine days later, the child took a severe tonsillitis; the temperature became continuous, the pulse rapid and a scarlet rash appeared. Finally, 58 days after the first injection of antitoxine, an undoubted antitoxine rash appeared. This case illustrates the difficulties in sometimes deciding the true nature of these rashes. In private practise, it is sometimes advisable to warn the nurse of the possibility of a rash, so that the parents need not be unnecessarily alarmed should such be discovered during convalescence.

OCCURRENCE OF "JOINT PAINS" AND "MUSCULAR PAINS"
following the use of Antitoxic Serum.

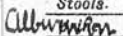
Both these are usually included under the term "Articular Pains", or "Joint Pains" in most textbooks. This is a mistake, for I am inclined to believe the muscular pain is much the more frequent, and that in a great majority of cases the pain is not in the joints at all, but in the muscles round the joints. These pains are always much more troublesome to the patients than the most profuse rash. They are, in addition, accompanied by a higher/

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Aged 13. Occupation



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higher rise of temperature, which is of longer duration. In most cases the pain is referred to as a "soreness", or "ache", or "stiffness" in the muscles around one or more of the larger joints, notably the knee, wrist, ankle or hip. Occasionally, patients complain of a back ache. I have never seen any swelling of the joints when the pain is apparently articular, nor do I know that such has been described in cases due to antitoxic serum alone.

Charts 13 and 14 show the more severe and prolonged pyrexia which usually accompanies the presence of these pains. In both these cases, the pain was muscular, and was apparently not very severe. Even gentle handling of the affected limbs produced complaint or tears.

Chart 15, however, is from a patient who suffered considerably. The rash which was of an urticarial nature, was at first very itchy and irritating. The pains in this case were articular and much more acute than is usually the case. The wrists were the joints most affected. Here again, as in many other cases, albuminuria appeared during the time the temperature was elevated.

As regards treatment, usually little is required. In more severe cases, treatment is difficult. Salicue/

Salicue and the Salicylates appear to do no good. Opium is contra-indicated where albuminuria is so frequently observed. Phenacetin and antipyrine are depressants and of doubtful value. Hot fomentations to the affected areas appear to give most relief. What effect the occurrence of these "pains" and "rashes" has on the chances of recovery of severe cases, is doubtful. In less severe cases, the pyrexia seen so often to ^{be} present, frequently greatly influences the pulse. The rate is often greatly increased and the pulse frequently becomes smaller. It is doubtful if the pulse is ever quite so good after the attacks as it may previously have been, but in the great majority of cases, the effects rapidly disappear. I have ^{not} been able to find any recorded case where serious harm has been known to follow these "after effects".

CAUSATION OF ANTITOXINE "RASHES", "PAINS", etc.

To the serum in which the antitoxine itself is contained, must be laid the blame of all the disadvantages of the antitoxic treatment of Diphtheria. Salter²¹ has shown that the blood serum of one animal exercised a toxic effect upon animals of another species. Experimentally, he has shown that/

that non-medicated serum, when injected into an animal of another species, causes a rise to temperature, and in some cases, the production of a rash.

From clinical observations, it would appear that rashes, etc., are more prevalent after the use of certain brands of serum than others. Moreover, when using the serum of one firm only, it is found the percentage of rashes varies considerably with serum made at different times. From this, it would appear if the preparation is the same (as it is stated to be) that the sera of different horses have a varying power of producing these toxic effects. Apparently a personal idiosyncrasy on the part of the patient is in some cases well marked. If the above statements are true, then the larger the amount of serum injected, the greater should be liability to severe effects. This as a rule appears to be so, but in some cases (such as case 12 p. 54) very large doses are given without any disagreeable result whatever.

CONCLUSIONS.

1. That the antitoxic treatment has considerably reduced the case mortality of diphtheria.
2. That the early administration of large doses is the key note of success.
3. That it is in cases of laryngeal diphtheria, that antitoxine has produced its most brilliant results.
4. That antitoxine has very greatly reduced the case mortality from laryngeal diphtheria.
5. That antitoxine has rendered operative interference less frequently necessary; and when necessary, less severe and much more likely to be attended with a successful result.
6. That the ill effects following the administration of antitoxine are either so very rare, or are of so mild a nature that they may be practically disregarded in the great majority of cases.
7. The fact that the total mortality is not appreciably altered since the introduction of antitoxine, must be ascribed to, the increased epidemic prevalence of the disease of late years, to its increased severity, or to the fact that antitoxine is not used energetically enough outside hospital practise, where the death rate everywhere, has of late years been higher than in hospital. Thus the death rate at the Edinburgh City Hospital last year was 7% /

7% the death rate outside was 16%.

My thanks are due to the following gentlemen, who in their capacity as Medical Officers of Health have kindly supplied me with statistics.

Sir Henry Littlejohn. Dr Chalmers, (Glasgow)
Dr. Hope (Liverpool) Dr Niven, (Manchester)
and Dr. Newsholme, (Brighton).

To Dr. C.B.Ker I am especially indebted for notes on several of the cases. While I can alone lay claim to the many shortcomings in the foregoing pages, any merit they may contain; (and I hope there is a little), is entirely due to the privilege I have had, of having been for nearly six months, a pupil to so courteous a master of the subject as Dr. Ker.

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